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The Inflammatory Potential of Diet and its Relationship with Metabolic, Mental, and Cardiovascular Health among Childhood Cancer Survivors: The St. Jude Lifetime Cohort Study (SJLIFE)

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DEDICATION

I dedicate this to my family and to my fiancé who have always given me unconditional love and support. This would not have been possible without you.

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ABSTRACT

Background: Diet is now known to play an important role in the process of inflammation and subsequent chronic health events, such as cancer, metabolic syndrome (MetS), anxiety, depression, and cardiovascular disease (CVD). The Dietary Inflammatory Index (DII®) and energy-adjusted DII (E-DII™) are tools that can estimate the inflammatory potential of diet of individuals. Previous research has focused predominantly on diet-associated inflammation and adverse health effects in populations that were not composed of cancer survivors. As of the time of this dissertation, none have focused on childhood cancer survivors. Childhood cancer survivors are at an elevated risk of suffering from an adverse chronic health event at an earlier age compared to the general population. The St. Jude Lifetime Cohort Study (SJLIFE) provides the unique opportunity to investigate potential associations between the inflammatory potential of diet and adverse chronic health problems among this group of survivors and controls. The purpose of this research is to explore the following associations: 1. Association between diet-associated inflammation and C-reactive Protein (CRP); 2. Association between diet-associated inflammation and Metabolic Health (hemoglobin A1C, HOMA-IR, fasting glucose, fasting insulin, waist circumference, high-density lipoproteins, triglycerides, and metabolic syndrome); 3. Association between E-DII and Mental Health (anxiety and depression); and 4. Association between diet-associated inflammation and Cardiovascular Health (hypertension,

hyperlipidemia, cardiomyopathy, coronary artery disease (CAD), cardiac dysrhythmia, and cerebrovascular accidents (CVA).

Methods: Data from SJLIFE among cancer survivors diagnosed between 1962 and 2012 we used to examine associations between diet-associated inflammation and adverse health outcomes among a cohort of childhood cancer survivors and controls. The E-DII who used in all analyses based on better model fit (lower AIC values). E-DII scores were computed using the 2005 Block Food Frequency Questionnaire (FFQ). The E-DII was analyzed as both as a continuous variable and categorized into quartiles where quartile 1 represents the most anti-inflammatory diet. First, we investigated the association between the E-DII and CRP among SJLIFE cohort members. CRP was analyzed as a continuous, binary (based on the cut-off 3mg/L), and categorical outcome (based on two cut-offs: <1 mg/L, 1-3 mg/L, and >3 mg/L). Second, we examined the associations between the E-DII and hemoglobin A1C, fasting glucose, fasting insulin, Homeostatic Model of Assessment of Insulin Resistance (HOMA-IR), waist circumference, high-density lipoproteins (HDL), triglycerides, and metabolic syndrome (MetS). Multivariable linear and logistic regression models were used to assess these associations. Third, the Brief Symptom Inventory-18 (BSI-18) was used to investigate acute symptoms of anxiety and depression. Multivariable linear and logistic regression models were used to evaluate the associations between the inflammatory potential of diet and symptoms of anxiety and depression. Fourth, we examined the associations between the E-DII and hypertension, hyperlipidemia, cardiomyopathy, coronary artery disease (CAD), cardiac dysrhythmia, and cerebrovascular accidents (CVA). Multivariable logistic models were used to investigate the associations between the E-DII and CVD outcomes. Results: Multivariable analysis revealed that the

inflammatory potential of diet is associated with insulin resistance (HOMA-IR) ($OR_{Quartile\ 4vs1}$ = 1.28, 95% CI: [1.13, 1.44]) and HDL cholesterol ($OR_{Quartile\ 4vs1,}$ = 1.23, 95 CI: [1.09, 1.38]). Multivariable analysis also revealed that diet-associated inflammation was not significantly associated with hs-CRP in this population. Multivariable analysis revealed that the E-DII was not associated with symptoms of anxiety. In contrast, multivariable analysis revealed that depressive symptoms were significantly associated with the E-DII as a continuous and categorical variable (OR =1.07, 95% CI: [1.02, 1.13]; $OR_{Quartile\ 4vs1}$ = 1.63, 95% CI: [1.19, 2.23], respectively). Age-adjusted logistic models revealed that the E-DII as a continuous variable was associated with hypertension (OR=1.06, 95% CI: [1.03, 1.10], and CAD (OR=1.14, 95% CI: [1.05, 1.24]. Age-adjusted logistic models revealed that a pro-inflammatory diet was associated with hypertension ($OR_{Quartile\ 4vs1}$ = 1.46, 95% CI: [1.17, 1.81]), and CAD ($OR_{Quartile\ 4vs1}$ = 1.97, 95% CI: [1.16, 3.35]). Multivariable logistic models revealed that the E-DII, as a continuous variable, was associated with a significantly lower odds of hyperlipidemia (OR=0.91, 95% CI: [0.86, 0.97]). Multivariable analysis showed that a pro-inflammatory diet was not significantly associated with hypertension, hyperlipidemia, cardiomyopathy, CAD, cardiac dysrhythmia, or CVA.

Conclusion: Results for the first aim is consistent with our hypothesis that diet plays an important role in regulating insulin resistance and HDL cholesterol levels. Results from the second aim indicates that diet-associated inflammation plays an important role in regulating depressive symptoms. Finally, results for the third aim reveals inconsistencies in the associations between the inflammatory potential of diet and CVD outcomes. Previous literature has shown that insulin resistance, low HDL levels, and depressive symptoms have the potential to increase the risk of CVD outcomes among childhood

cancer survivors and controls. Using intervention strategies that promote an anti-inflammatory diet to decrease the risk insulin resistance, HDL, and depression has the potential to decrease incidence and mortality from CVD observed among childhood cancer survivors. Analyses of longitudinal data collected over long time periods are needed to better understand these associations. These studies and, perhaps, others need to investigate biological mechanisms behind these associations.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

CHAPTER 1

INTRODUCTION

Childhood cancer is the second leading cause of death for children 5-14 years old in the United States (US) (Ward, DeSantis, Robbins, Kohler, & Jemal, 2014). In the US, incidence of childhood cancer has steadily increased at an annual rate of 0.6% since 1975 (Ward et al., 2014). However, within the same time period mortality has steadily declined by over 50% (Ward et al., 2014). As can be clearly deduced from these statistics, survival following a diagnosis of childhood cancer has improved dramatically over the past five decades (Armstrong et al., 2016; Ries, Pollack, & Young, 1983; Turcotte et al., 2017), with 5-year survival rates exceeding 84% in the US (Armstrong et al., 2016; Bethesda, 2015). Consequently, the number of childhood cancer survivors is estimated to be in excess of 500,000 in the United States by 2020 (Armstrong et al., 2016; Robison & Hudson, 2014). This increase in the size of the childhood cancer survivor population is largely due to the success of multimodal therapy (chemotherapy, radiotherapy, surgery, and supportive care) (Armstrong et al., 2016; Green et al., 2013; Hudson et al., 2012). Despite these advances, 5-year childhood cancer survivors remain at risk of progression or recurrence of their primary cancer and are at an elevated risk of new malignant neoplasms (second primaries), functional impairments, and other chronic diseases for the remainder of their lives

(Armstrong et al., 2016, 2014; Cardous-Ubbink et al., 2004; Dowling et al., 2010; M. C. Hoffman et al., 2013; Hudson, Jones, Boyett, Sharp, & Pui, 1997; Hudson, Ness, Gurney, Mulrooney, Chemiatilly, et al., 2013; Kadan-Lottick et al., 2010; Kurt et al., 2012; F. P. Li, Myers, Heise, & Jaffe, 1978; Mertens et al., 2008; Mertens, Neglia, & Potter, 2001; Moller et al., 2001; Ness et al., 2013; Oeffinger et al., 2006; S. M. Phillips et al., 2015; Pui et al., 2003; Reulen et al., 2010; Robison & Hudson, 2014; Tai et al., 2012; Zeltzer et al., 2009). Data from the St. Jude Lifetime Cohort Study (SJLIFE), a study of just below 6,000 individuals diagnosed with childhood cancer between 1962 and 2012, and who survived at least five years from their original cancer diagnosis, indicates that by age 45 years old, 95% of childhood cancer survivors will have at least one chronic condition, and 80% will have a severe, disabling or life threatening chronic condition (F. F. Zhang & Parsons, 2015). This is in contrast to data from the general population in the US where chronic disease prevalence rate is approximately 45% (Raghupathi & Raghupathi, 2018).

1.1 Lifestyle Factors

Empirical evidence indicates that childhood cancer survivors adopt unhealthy lifestyle behaviors (poor diet, low physical activity, smoking, alcohol consumption) and tend to gain excess weight following successful treatment at rates higher than their general population counterparts; and these behaviors can contribute to the excess morbidity and mortality (Gawade et al., 2015; Ness, Leisenring, Huang, et al., 2009; F. F. Zhang et al., 2018).

Survivors of childhood cancer are consistently observed to consume diets that are low in fruit, vegetable, and calcium and high in fat (Stolley, Restrepo, & Sharp, 2010; F. F. Zhang et al., 2018; F. F. Zhang & Parsons, 2015). Previous research in the SJLIFE has

examined the diet quality of childhood cancer survivors using the Healthy Eating Index (HEI)-2015, where a higher score indicates better diet quality. The average score among survivors was 60.1 out of 100 (F. F. Zhang et al., 2018). The average age of these cancer survivors was 32.3 years old (F. F. Zhang et al., 2018). Data from the National Health and Nutrition Examination Survey (NHANES) from 2015-2016 indicates that in the general population the average HEI-2015 score of adults 18-64 years old is lower (58.3) compared to childhood cancer survivors (USDA, n.d.). This is consistent with other studies evaluating diets among childhood cancer survivors that observe inadequate nutritional intake (Landy et al., 2013; Onvani, Haghighatdoost, Surkan, Larijani, & Azadbakht, 2017; F. F. Zhang et al., 2019; F. F. Zhang, Saltzman, et al., 2015). Consumption of inadequate diets place childhood cancer survivors at greater risk for detrimental health conditions compared to individuals in the general population (F. Zhang, Liu, Esther, Must, & Denmark-Wahnefried, 2015).

Physical activity (PA) also contributes to an individual's overall health (Rogers, Colbert, Greiner, Perkins, & Hursting, 2008; Stolley et al., 2010). These benefits include improved physical functioning, reduced fatigue, and weight loss (McTiernan, 2004). There is a large body of evidence suggesting that increased levels of PA are protective against several different types of chronic conditions (e.g. obesity, CVD, diabetes, hypertension, cancer, mortality) (Rogers et al., 2008; Stolley et al., 2010). Evidence shows that survivors of childhood cancer tend to report low levels of PA, especially during adulthood. Among this group of survivors, fewer than 50% report adequate levels of PA (Castellino et al., 2005; Demark-Wahnefried et al., 2005; Florin et al., 2007; Hudson et al., 2002; Ness, Leisenring, Huang, et al., 2009; Stolley et al., 2010).

Tobacco smoking is one of the most modifiable and preventable risk factors implicated in development of detrimental chronic conditions (Butterfield et al., 2004; Demark-Wahnefried et al., 2005; Gawade et al., 2015; Kasteler et al., 2019). Smoking significantly increases the risk of cancer recurrence and second primary cancers (Carretier et al., 2016). Currently, approximately 22% of childhood cancer survivors smoke cigarettes (Huang et al., 2018). This corresponds to a larger proportion survivors that smoke cigarettes compared to the general population in the US (13.7%) (CDC, 2019). Tobacco use has the potential to increase the risk of radiation used during treatment. For example, among Hodgkin lymphoma childhood cancer survivors the risk of radiotherapy-induced lung cancer is higher among tobacco consumers (Carretier et al., 2016; Elliot, Lindemulder, Goldberg, Stadler, & Smith, 2013).

Although light to moderate alcohol use has exhibited a protective effect on some adverse health conditions, alcohol abuse promotes the onset of cancer and chronic disease. Alcohol use is recognized to increase the risk of second primary malignancies among cancer survivors and in the general population (Carretier et al., 2016; Travis et al., 2002). Younger childhood cancer survivors tend to display lower levels of alcohol use compared to the general population; in contrast, older survivors tend to display higher levels of alcohol consumption (Carretier et al., 2016).

A poor diet can lead to a state of chronic inflammation through inhibition of anti-inflammatory cytokines resulting in a wide array of detrimental health effects (Khan et al., 2018; Ramallal et al., 2017; Saita, Kondo, & Momiyama, 2014). These adverse health effects include the early onset of chronic conditions such as metabolic syndrome (MetS), anxiety, depression, and cardiovascular disease (CVD) (Chow et al., 2015; Scott, Latha, &

Aruna, 2015; Zeltzer et al., 2009). Among childhood cancer survivors, cancer therapies such as chemotherapy and radiation, have been discovered to activate certain pathways that have the potential of leading to hormone deficiencies, production of inflammatory mediators, lipid metabolism, changes in insulin activity, and adipokines (Scott et al., 2015). Cardiovascular disease (CVD) is now recognized as a leading contributor to morbidity and mortality among childhood cancer survivors (Chow et al., 2015). Survivors of specific primary cancers (i.e., lymphomas, neuroblastomas, acute lymphoblastic leukemia, and testicular tumors) have been observed to display clinical features of MetS (Gurney et al., 2006; K. E. Hoffman et al., 2008; Link et al., 2004; Nuver et al., 2005; Scott et al., 2015).

1.2 Inflammation

Inflammation, which provides a substrate for enzyme action in a number of metabolic mechanisms, is regulated by numerous intrinsic and environmental factors (Khan et al., 2018; Maihöfner et al., 2003; McCullough et al., 2017; Neumann et al., 2014; Shehzad, Subhan, & Lee, 2011). Acute inflammation is a normal response to an infection, injury or even a new cancer that involves an immune response (Elenkov, Iezzoni, Daly, Harris, & Chrousos, 2005; Kiecolt-Glaser, Derry, & Fagundes, 2015). Although acute inflammation is a normal and beneficial process, chronic inflammation has been identified as a risk factor for cancer (Crusz & Balkwill, 2015), and other chronic health conditions such as obesity (Saltiel & Olefsky, 2017), depression (Faugere et al., 2017), anxiety (Renna, O'Toole, Spaeth, Lekander, & Mennin, 2018), cardiovascular disease (Lopez-Candales, Hernández Burgos, Hernandez-Suarez, & Harris, 2017), and frailty (Ferrucci & Fabbri, 2018). Acute inflammation requires the negative feedback signaling from anti-inflammatory cytokines needed to discontinue the response (Elenkov et al., 2005; Khan et

al., 2018; Kiecolt-Glaser et al., 2015). In contrast, chronic inflammation lacks this vital negative feedback signaling (Elenkov et al., 2005; Khan et al., 2018; Mathé et al., 2012). Diet is now recognized as an important regulator of chronic inflammation (F. F. Zhang & Parsons, 2015).

1.3 The Dietary Inflammatory Index (DII®)

The DII® is a tool that was developed in order to measure the inflammatory potential of person's diet. The DII quantifies an individual's dietary intake on a continuous scale ranging from maximally anti-inflammatory to maximally pro-inflammatory based on a refined scoring algorithm of peer-reviewed articles published from 1950-2010 (Shivappa, Steck, Hurley, Hussey, & Hebert, 2014). Across several populations it has been observed that a decreasing DII score, indicating an anti-inflammatory diet, is associated with increasing energy (caloric) intake. This led to the development of the Energy Density- DII (E-DII™) (Khan et al., 2018). The DII and now the E-DII have since been construct validated many (25) times against several inflammatory biomarkers in various populations (Bodén et al., 2017; Julia et al., 2017; Kizil et al., 2016; Kotemori et al., 2018; Mayr et al., 2018; Na, Kim, & Sohn, 2018; C. M. Phillips, Shivappa, Hébert, & Perry, 2018a; Sen et al., 2015; Shivappa, Hebert, Marcos, et al., 2017; Shivappa, Hébert, et al., 2015; Shivappa, Steck, et al., 2015; Shivappa, Wirth, Hurley, & Hebert, 2017; Shivappa, Wirth, Murphy, Hurley, & Hebert, 2018; Tabung et al., 2015; Vahid et al., 2018; Vahid, Shivappa, Hekmatdoost, et al., 2017; M. D. Wirth, Shivappa, Davis, et al., 2017). Differences in dietary requirements between children and adults led to the development of the Children's Dietary Inflammatory Index (C-DII™). The C-DII is a novel tool for assessing diet driven inflammation among children that can be applied to children from various distinct

populations where sufficient dietary information has been collected. Future research can use the C-DII to assess dietary intake of children with cancer (Khan et al., 2018).

1.4 St. Jude Lifetime Cohort

The St. Jude Lifetime Cohort Study (SJLIFE), a lifetime cohort of childhood cancer survivors who were treated at SJCRH. The SJLIFE cohort was created to (i) investigate the health of adult childhood cancer survivors, (ii) reduce the late effects of childhood cancer treatments, (iii) create recommendations for the treatment and follow-up of individuals treated for childhood cancers, and (iv) guide health promoting interventions. A detailed description of the SJLIFE cohort is presented below (Hudson et al., 2011). Recruiting individuals who were treated at SJCRH facilitates prospective medical assessment of health outcomes among childhood cancer survivors in adulthood. Survivors have >5 years of survival from the time of diagnosis (Howell et al., 2020). SJLIFE offers three levels of participation: (1) comprehensive evaluation on SJCRH campus; (2) local evaluation by Examination Management Services, Inc. (EMSI); or (3) completion of health surveys by phone interview or by mail (Howell et al., 2020; Hudson et al., 2011).

1.5 Rationale & Aims

The successful treatment of childhood cancers provides the scientific community with an opportunity and the responsibility to evaluate the long-term health of this population. The late effects of therapy for childhood cancers are commonly reported amongst survivors (Hudson, Ness, Gurney, Mulrooney, Chemaitilly, et al., 2013; Hudson et al., 2011; Mertens et al., 2008; Reulen et al., 2010). Although the body of literature on childhood cancer survivors is growing, there are still many gaps regarding the long-term survival of these individuals. The majority of institutions focusing on this group lack the

resources, infrastructure, or flexibility to perform comprehensive research investigations on a large enough group of survivors (Hudson et al., 2011). This makes SJCRH a unique institution for investigating late outcomes in childhood cancer survivors. SJCRH has another research cohort, the Childhood Cancer Survivorship Study (CCSS) (Mertens et al., 2008). Although this other cohort has provided important insights into the long-term health of childhood cancer survivors, this study depends exclusively on self-report methodology (Mertens et al., 2008). In contrast, the SJLIFE cohort is a lifetime cohort of survivors in which many participants have undergone comprehensive clinical evaluations. Knowledge gained from research on this group of childhood cancer survivors has the potential to: improve the quality of life among childhood cancer survivors and their families, guide healthcare providers in developing new treatments, monitor the long-term health of survivors, and facilitate the approval of screening and other services by legislators and insurance companies (Hudson et al., 2011).

The following are the Specific Aims of this dissertation:

(1) Investigate the cross-sectional associations between DII scores and markers of inflammation and metabolic health among childhood cancer survivors and controls

(2) Identify the cross-sectional associations between DII scores and adverse mental health outcomes (depression and anxiety) among childhood cancer survivors and controls

(3) Identify the cross-sectional associations between DII scores and cardiovascular disease (CVD) among childhood cancer survivors and controls

1.6 Dissertation Framework

Chapter 2 of my dissertation will explore the literature relating to childhood cancer, childhood cancer survival, and the late effects of treatment following diagnosis. This will include the types of childhood cancers, treatments for childhood cancers, adverse health risk following survival, and chronic inflammation among childhood cancer survivors. Chapter 3 details the methodology used throughout this dissertation, how information was obtained from survivors, and the statistical framework used. Chapter 4 investigates the relationship between DII scores and Markers of Inflammation and Metabolic health. Chapter 5 investigates the relationship between DII scores and Mental Health (anxiety & depression). Chapter 6 investigates the relationship between DII scores and Cardiovascular Disease (CVD). And finally, Chapter 7 will discuss the process, findings, and implications of this dissertation in detail.

CHAPTER 2

LITERATURE REVIEW

2.1 Childhood cancer

There are over 100 different cancers classified by morphology, anatomic location, histopathology, and immune chemistry (Kleinsmith, 2006). Despite differences across subtypes, there are 6 hallmarks of cancer; sustaining proliferative signaling, evading growth suppressors, resisting cell death (apoptosis), enabling replicative immortality, inducing angiogenesis, and activating invasion and metastasis (Hanahan & Weinberg, 2000; Kleinsmith, 2006). These converge on a final description of cancer that is well known; uncontrolled growth of abnormal cells (Bertram, 2001; Kleinsmith, 2006; Papaccio et al., 2017). Normally, the human body is comprised of approximately 10^{15} cells that divide and differentiate for the purpose of repopulating organs and tissues. Old cells undergo apoptosis (i.e., programmed cell death) and are constantly replaced by newly formed cells (Bertram, 2001; Kleinsmith, 2006; Papaccio et al., 2017). Stem cells are the only type of cells that have the ability to divide and replace old cells (Bertram, 2001; Kleinsmith, 2006; Papaccio et al., 2017). This normal mechanism is hindered by the ability of cancer cells to reproduce uncontrollably while delaying or avoiding cell death. Furthermore, this problem creates an excess of cells that interfere with normal organ function or promote the displacement of normal cells (Bertram, 2001; Kleinsmith, 2006; Papaccio et al., 2017).

2.2 Types of Childhood Cancer

Leukemia

Leukemias are cancers that arise among cells responsible for blood formation in the bone marrow (Kleinsmith, 2006). Leukemia is characterized by the large accumulation of immature and abnormal white blood cells (WBCs) in the bloodstream. Classification is based on the cell type and the rate of progression; i.e., acute versus chronic (Kleinsmith, 2006). Chronic leukemias are characterized by cancerous cells that are mature and retain normal functions, leading the disease to exhibit a slow progression. Acute leukemias are characterized by cancerous cells that are immature and cannot function properly, leading to the exponential increase in the number of cancer cells and a fast progression of the disease (Jin, Xu, An, & Wang, 2016). Cancer cells found in acute leukemias tend to appear more abnormal compared to cells found in chronic leukemias (Kleinsmith, 2006). Leukemias arise from two different types of white blood cells called lymphoid cells and myeloid cells. The four primary types of leukemias are acute lymphoblastic leukemia (ALL), chronic lymphoblastic leukemia (CLL), acute myeloid leukemia (AML), and chronic myeloid leukemia (CML) (Jin et al., 2016).

Leukemias are the most common form of childhood cancer accounting for approximately 30% of all cancers diagnosed in children less than 15 years old (Bernard, Abdelsamad, Johnson, Paisley, Chapman, & Parvathaneni, 2017; Jin et al., 2016; Kleinsmith, 2006). Cases of childhood leukemia are typically acute, whereas both acute and chronic cases are frequently observed in adults (Barrington-Trimis et al., 2017; Bernard et al., 2017). According to the National Cancer Institute's SEER population-based registry from 2009 to 2013, a total of 5,443 cases of childhood leukemia were reported in

the United States. During this time childhood leukemia had the highest incidence among Hispanic White children (6.05 per 100,000) followed by non-Hispanic White children (4.45 per 100,000), non-Hispanic Asian children (4.21 per 100,000), and non-Hispanic Black children (2.62 per 100,000) (Barrington-Trimis et al., 2017). The Global Burden of Disease Study (GBD) estimates that, worldwide, the number of incident cases of all types of childhood (0-14 years) leukemia was 63,230 in 2016 (Bhakta et al., 2019).

Acute Lymphoblastic Leukemia

ALL is characterized by the abnormal proliferation and differentiation of lymphoid progenitor cells from the blood, bone marrow, and extramedullary locations (Teachey & Pui, 2019; Terwilliger & Abdul-Hay, 2017). ALL can be broadly classified into two main types based on immunophenotype, B-cell and T-cell ALL (Teachey & Pui, 2019; Terwilliger & Abdul-Hay, 2017). Childhood cases of ALL account for approximately 80% of total cases (Terwilliger & Abdul-Hay, 2017). The Global Burden of Disease Study (GBD) estimates that worldwide the number of incident cases of childhood (0-14 yrs) ALL was 30,089 in 2016 (Bhakta et al., 2019). Developments in treatments over decades has increased the 5-year survival time of children with ALL to above 90% (Mulrooney et al., 2019; Pui et al., 2009). This group comprises approximately 16% of all long-term survivors of childhood cancer (Mulrooney et al., 2019; Robison & Hudson, 2014). However, T-cell ALL has been consistently observed to have poorer outcomes compared to B-cell ALL among this population (Mulrooney et al., 2019; Robison & Hudson, 2014).

Acute Myeloid Leukemia (AML)

AML is characterized by the clonal expansion of myeloid progenitor cells, also called blasts, in the blood and bone marrow (Saultz & Garzon, 2016). The overall cure rate for AML is estimated to be between 35-40% among individuals <60 years old (Saultz &

Garzon, 2016). Childhood AML makes up approximately 18% of all childhood leukemia cases and contributes to approximately 50% of all childhood leukemia deaths in the United States (Hossain, Xie, & Caywood, 2015). The GBD estimates that worldwide the number of incident cases of childhood (0-14 yrs) AML was 11,631 in 2016 (Bhakta et al., 2019). The age-adjusted incidence rate of childhood AML has been increasing by approximately 1% each year from 1975 to 2011. The incidence is currently estimated to be about 8.5 cases per million at risk children (Hossain et al., 2015).

Leukemias that are rare in children

Cases of CML are rare among children and are readily treatable (Seth & Singh, 2015). CML typically occurs in middle age having a peak incidence that tends to be between 40-50 years of age (Seth & Singh, 2015). However, cases are observed among infants and young children (Seth & Singh, 2015). Two main types of chronic myelogenous leukemias are currently recognized and occur at different age ranges among children. The first type is clinically comparable to adult CML and occurs after 4 years of age. This type of CML typically accounts for a small proportion of the childhood cancer cases (3-5%) (Seth & Singh, 2015).

Juvenile Chronic Myelogenous Leukemia (JCML), occurs in infancy through early childhood usually in children under 4 years old and progresses much more rapidly than CML (Seth & Singh, 2015). JCML, also called juvenile myelomonocytic leukemia, accounts for <2% of childhood leukemias (Seth & Singh, 2015). JCML commonly presents with lymphadenopathy, anemia, infection, hepatosplenomegaly, skin conditions (eczema, xanthoma and café-au-lait spots), and thrombocytopenia (Seth & Singh, 2015). JCML is very severe and is rapidly fatal. Treatment typically involves treatment of infections, red

blood cell (RBC) and platelet transfusions, and stem cell transplant from matched sibling donors (if possible). Event-free survival at 3 years old is between 30-50% (Seth & Singh, 2015).

Lymphoma

Lymphomas are cancers arising from cells of the lymphatic system (Kleinsmith, 2006). Lymphomas can occur almost anywhere in the body since lymphatic tissue is distributed throughout its entirety (Shanbhag & Ambinder, 2018). B lymphocytes and T lymphocytes are the main cells of the lymphatic system (Shanbhag & Ambinder, 2018). B lymphocytes develop into plasma cells that produce immune proteins, called antibodies, that protect the body from infectious agents (Shanbhag & Ambinder, 2018). T lymphocytes are directly involved in destroying bacteria and foreign or abnormal cells; they also assist the function of other immune system cells (Shanbhag & Ambinder, 2018). Lymphomas can be subdivided into two main types: Hodgkin Lymphoma (HL) and non-Hodgkin Lymphoma (NHL) (Shanbhag & Ambinder, 2018). Cases of NHL are seen more commonly compared to HL. HL accounts for approximately 10% of all lymphoma cases, NHL accounts for the remainder of cases (90%) (Shanbhag & Ambinder, 2018). The number of deaths from all lymphoma is estimated to exceed 21,000 in the United States (Shanbhag & Ambinder, 2018). NHL is responsible for a significantly greater proportion of lymphoma deaths compared to HL, 95% and 5%, respectively (Shanbhag & Ambinder, 2018). NHL can arise from both T lymphocytes and B lymphocytes, 15% and 85%, respectively (Kleinsmith, 2006).

Lymphomas are the third most common malignancy among children and adolescents. In children under 15 years of age, non-Hodgkin Lymphoma (NHL) cases are

more common. However, in patients under 18 years of age, Hodgkin disease is the most common (Allen, Kelly, & Bollard, 2020; Uzunova & Burke, 2015). Lymphoma is the most common cancer diagnosis among adolescents (15-19 years old). Almost two-thirds of cases in the group are HL (Shanbhag & Ambinder, 2018).

Hodgkin Lymphoma

HL is characterized by a unique class of abnormal B lymphocytes called Reed-Sternberg cells (Kleinsmith, 2006). Cells of this type are significantly larger than normal lymphocytes and appear different from the cells of NHL as well as the cells of other cancers (Kleinsmith, 2006). Reed Sternberg cells are often positive for the Epstein-Barr Virus (EBV) in developing countries. This virus is seldom observed in HL cases in North America and Western Europe. Epstein-Barr is a gamma herpesvirus generally spread through the saliva and is responsible for the development of infectious mononucleosis. Individuals with infectious mononucleosis are at an elevated risk of developing EBV-positive HL (RR 4.0; 95% CI 3.4-4.5). HL can be subdivided into two types: classical HL (cHL) and nodular lymphocyte-predominant HL (NLPHL) (Shanbhag & Ambinder, 2018). The five-year survival rate of individuals <20 years of age with HL is estimated to exceed 96% in the United States (Wogksch et al., 2018). The GBD estimates that worldwide the number of incident cases of childhood (0-14 yrs) HL was 5,220 in 2016 (Bhakta et al., 2019). HL can be diagnosed in 1 of 4 stages: (I) HL is found in 1 lymph node area or lymphoid organ or is found only in one part of one organ outside the lymphatic system, (II) HL is found in two or more lymph node areas on the same side or HL extends locally from one lymph node area into a nearby organ, (III) HL is found in lymph node areas on both sides of diaphragm (above and below) or HL is in lymph nodes above the diaphragm and

in the spleen, and (IV) HL has spread widely into at least one organ outside of the lymph system (ACS, 2018b).

Non-Hodgkin Lymphoma

NHL is the most common type of lymphoma observed among children. However, NHL is very rare in children under 3 years old (Uzunova & Burke, 2015). The 5-year survival rate of childhood NHL has been steadily improving over the decades and is now estimated to be >85% (Ehrhardt et al., 2017). The GBD estimates that worldwide the number of incident cases of childhood (0-14 yrs) NHL was 17,350 in 2016 (Bhakta et al., 2019). The peak incidence for NHL is in the second decade of life (10-20 years) (Uzunova & Burke, 2015). NHL represents a diverse group of immune system cancers (Armitage, Gascoyne, Lunning, & Cavalli, 2017). NHL among children differs in comparison to NHL among adults. Adults typically experience low to intermediate-grade lymphomas. NHL can be diagnosed in one of four stages in children: (I) NHL is only in one place (single tumor not in lymph nodes or in lymph nodes in one part of the body) and not in the chest or abdomen, (II) NHL is a single tumor in nearby lymph nodes in only one part of the body or NHL is more than one tumor and/or in more than one set of lymph nodes or the NHL started in the digestive tract, (III) NHL started in the chest or abdomen (spread too widely in abdomen to be treated with surgery) or is located next to the spine or is more than one tumor or in more than one set of lymph nodes, and (IV) NHL is in the central nervous system (CNS) (ACS, 2017b). In contrast, children are often diagnosed with high grade lymphoma. The World Health Organization (WHO) has classified NHLs on the basis of differentiation (precursor vs mature) and phenotype (NK vs T- vs B-cell) (Allen et al., 2020). There are four subtypes of childhood lymphoma that represent approximately 90%

of cases: Burkitt's Lymphoma (BL), diffuse large B-cell lymphoma (DLBCL), lymphoblastic lymphoma (LBL) (precursor T- and B-cell lymphoma), and anaplastic large-cell lymphoma (ALCL) (Allen et al., 2020; Uzunova & Burke, 2015). Cutaneous, Follicular, and peripheral T-cell Lymphomas represent the remaining 10% (Uzunova & Burke, 2015).

BL is typically a highly aggressive tumor that represents approximately 30% of total childhood NHL cases in the United States (Allen et al., 2020; Sandlund, Downing, & Crist, 1996). BL is most commonly found within the lymph nodes and abdomen, although it can be found at other sites around the body (Allen et al., 2020; Mbulaiteye, Biggar, Bhatia, Linet, & Devesa, 2009). BL contains malignant cells that show a mature B-cell phenotype (Allen et al., 2020; Sandlund et al., 1996). DLBCL represents between 10-20% of NHL cases among children and adolescents. It is also having a mature B-cell phenotype. LBL is generally a precursor T-cell lymphoma; however, rare cases of precursor B-cell lymphoma have been diagnosed among children (Allen et al., 2020). LBL is the second most common type of childhood NHL, accounting for between 25-35% of all cases. The majority of cases of LBL are of T-cell origin (70-80%) while 20-25% are of B-cell origin (Burkhardt & Hermiston, 2019). ALCL accounts for approximately 10% of childhood NHL cases (Allen et al., 2020; Burkhardt et al., 2005). The NHL phenotype is predominantly mature T-cell but null-cell disease (no NK, T-, or B-cell surface antigens expressed) is rarely observed (Allen et al., 2020; Jaffe, Harris, Stein, & Isaacson, 2009).

Central Nervous System Tumors

CNS tumors are characterized by the formation of new abnormal cells that originate in the brain, spinal cord, cranial and spinal nerves, and sellar region (located below the brain in the center of cranial base) (Scheie et al., 2019). The WHO classifications identifies more than 130 different CNS tumors. These include gliomas, meningiomas, mesenchymal tumors, melanocytic tumors, lymphomas, histiocytic neoplasms, germ cell tumors, and other often rare forms of the disease (Scheie et al., 2019). A majority of CNS tumors arise from glial cells. These tumors, or gliomas, can originate from several distinct types of glial cells (Chlebik, 2019; Kleinsmith, 2006). The most common type of glial cells are called astrocytes. These cells are responsible for the development of astrocytomas (Kleinsmith, 2006). CNS tumors arising from other cells are very rare among adults but are commonly diagnosed in children. The most common type of CNS tumor arising from non-glial cells is called medulloblastoma (Kleinsmith, 2006). This type of tumor is classified as an embryonal tumor and arises from a primitive neural cell that is typically found in the cerebellum (Kleinsmith, 2006). In 2015, CNS tumors accounted for 1.4% of all newly diagnosed cancer cases and 2.6% of cancer deaths (McNeill, 2016).

CNS tumors are the most common type of solid tumor found among children and second most common type of childhood malignancy (Chlebik, 2019; Kleinsmith, 2006; McNeill, 2016). CNS tumors represent approximately 20% of all childhood cancer cases (Chlebik, 2019; Kleinsmith, 2006). CNS tumors are estimated to account for 20% and 30% of cancer deaths among children and young adults, respectively (McNeill, 2016). The GBD estimates that worldwide the number of incident cases of childhood (0-14 years) CNS tumors was 29,967 in 2016 (Bhakta et al., 2019). The most common types of CNS tumors

found in children are pilocytic astrocytoma, embryonal tumors, and malignant gliomas (McNeill, 2016). Approximately 50% of childhood brain tumors are gliomas (Ezzat et al., 2016; Harmouch, Taleb, Lasseini, Maher, & Sefiani, 2012; Kaderali, Lamberti-Pasculli, & Rutka, 2009; McNeill, 2016; Rosemberg & Fujiwara, 2005). The majority of gliomas found in children are either pilocytic astrocytoma or other low-grade gliomas (Ezzat et al., 2016; Harmouch et al., 2012; Kaderali et al., 2009; McNeill, 2016; Rosemberg & Fujiwara, 2005). Embryonal tumors, such as medulloblastomas, arise from embryonal cells in the brain. These tumors can be benign or malignant, with childhood tumors being predominantly malignant (Chlebik, 2019; NCI, 2018). CNS tumors are classified as grade I or II if tumors tend to grow slowly and have a low probability of invading nearby tissue and grade III or IV if the tumor grows quickly and has a high probability of spreading to nearby tissues (ACS, 2018h).

Astrocytoma/Glioma

Gliomas among children have a bimodal incidence, with the highest incidences at 6 and 13 years of age (Chlebik, 2019). The WHO classifies gliomas into 4 subtypes: grade I (pilocytic astrocytomas), grade II (diffuse or low-grade astrocytomas), grade III (anaplastic astrocytomas), and grade IV (glioblastoma multiforme (GBM)) (Chlebik, 2019; El-Ayadi et al., 2017). Childhood gliomas are predominantly grade I or II, this differs from adult gliomas that are predominantly grade III and grade IV. Among children, high-grade gliomas represent approximately 20% of all CNS tumors. GBM accounts for approximately 3% of childhood CNS tumors (Chlebik, 2019; Murphy, Poppe, & Jalali, 2018). Astrocytomas are typically low-grade tumors that are benign and can be cured through surgical resection (Chlebik, 2019; Chumas, Picton, Simmons, & Parulekar, 2016).

Pilocytic astrocytomas are the most prevalent childhood brain tumor that is commonly found in the posterior fossa (including cerebellum and brainstem), hypothalamus, or optic pathways (Chlebik, 2019; Scheie et al., 2019). These tumors represent approximately 17% of childhood CNS tumors. The 10-year survival of patients who undergo a total surgical resection is estimated to exceed 90% (Chlebik, 2019; Murphy et al., 2018; Vaidya, Smee, & Williams, 2012). Children who receive subtotal resections have a lower 10-year survival, 65-75% (Chlebik, 2019; Murphy et al., 2018; Suh & Mapstone, 2001).

Medulloblastoma

Medulloblastomas represent approximately 20% of all childhood CNS tumors. This form of cancer can spread from the brain to the spine (drop metastases). This type of metastases occurs mainly (i.e., with 70% of cases diagnosed) before 10 years of age and most cases occur between 5-8 years old (Chlebik, 2019). Medulloblastomas are categorized into 3 types: classic, nodular desmoplastic, and large cell anaplastic histology (Bhatia & Pruthi, 2018; Chlebik, 2019; Massimino et al., 2016; Paulino & Carrie, 2017). The most common types is classic medulloblastoma. Nodular desmoplastic tumors account for 7% of medulloblastomas and have the best outcomes out of the three. These tumors are the most common subtype among infants (<1 year old) (Chlebik, 2019; Massimino et al., 2016; Paulino & Carrie, 2017). Large cell anaplastic tumors have the worst prognosis. Among these tumors, 20-30% have undergone drop metastases at the time of diagnosis (Chlebik, 2019; Chumas et al., 2016; NCI, 2018; Wells & Packer, 2015).

Ependymoma

Ependymomas represent approximately 10% of all childhood brain tumors and is the third most commonly reported tumor found in children (Chlebik, 2019; Chumas et al.,

2016; Furtado, Panigraphy, & Fits, 2016; Suh & Mapstone, 2001). Although ependymomas can occur anywhere in the CNS, approximately 90% of these tumors are found within the cranium (Bhatia & Pruthi, 2018; Chlebik, 2019; Chumas et al., 2016; Furtado et al., 2016; Vaidya et al., 2012). Among children, these tumors occur most often in the posterior fossa, whereas this type of tumor is usually located in the intraspinal region among adults (Chlebik, 2019; Louis et al., 2016; Scheie et al., 2019). In addition, ependymomas found in the supratentorial compartment also are more common in children compared to adults (Pajtler et al., 2015; Scheie et al., 2019). The incidence of ependymomas decrease with age. Cases of ependymomas is the most common among infants and children under the age of 4 (Chlebik, 2019; Wells & Packer, 2015). The WHO categorizes ependymomas into the following subtypes: subependymoma (grade I), myxopapillary ependymoma (grade I), ependymoma (grade II), and anaplastic ependymoma (grade III) (Louis et al., 2016; Scheie et al., 2019). The 5-year survival rate of individuals under 19 years old is approximately 75% (Thorp & Gandola, 2019).

Primitive neuroectodermal tumors (PNETs)

PNETs are no longer recognized as a distinct type of CNS tumor according to the WHO 2016 classification (Louis et al., 2016; Scheie et al., 2019). The 2007 WHO classification identified this type of CNS tumor that originates in undifferentiated or poorly differentiated neuroepithelial cells that are found in the cerebrum, spinal cord, or brain stem (Scheie et al., 2019). Medulloblastomas and PNETS have similar histological characteristics. However, these tumors vary in their location, with medulloblastomas developing in the posterior fossa and PNETs developing the supratentorial region

(McNeill, 2016). Empirical evidence suggests that PNETs can be reclassified into other diagnostic subtypes (Louis et al., 2016; Scheie et al., 2019; Sturm et al., 2016).

Sarcomas

Sarcomas are malignant tumors that develop in connective supporting tissue and can be found anywhere on the body (Kleinsmith, 2006). This type of cancer represents approximately 1% of all cancer cases (Kleinsmith, 2006). There are two types of sarcomas: soft tissue sarcomas (STS) and bone sarcomas (BS) (Kleinsmith, 2006). STS are tumors found in muscle, fat, blood vessels, fibrous tissue, tendons, and cartilage (Kleinsmith, 2006). The most common type of BS are called osteosarcomas (OS) (Kleinsmith, 2006). These tumors develop in developing bone cells (Kleinsmith, 2006). Ewing's sarcoma (ES) is another form of bone cancer that arises from immature nerve tissue in the bone marrow (Kleinsmith, 2006). Most cases of Ewing's sarcoma and osteosarcoma occur among children and adolescents (Kleinsmith, 2006). Malignant bone tumors represent approximately 3% of tumors among children and adolescents (Jackson, Bittman, & Granowetter, 2016).

Ewing sarcoma (ES) family of tumors

ES is a round cell tumor arising from the bone (Battacharjee, Venkata, & Uppin, 2018; Jackson et al., 2016; W.-Y. Li, Brock, & Saunders, 2005). This form of cancer is the second most common type of bone tumor reported in children (Battacharjee et al., 2018; Jackson et al., 2016; W.-Y. Li et al., 2005). There are three types of ES: Ewing sarcoma of the bone (EWS), extra-skeletal Ewing sarcoma, and Askin tumor. These tumors represent what is called the Ewing sarcoma family of tumors (ESFT). PNET was formally classified as part of this family, however, the WHO 2016 classification no longer recognizes PNET

as distinct type of tumor (Scheie et al., 2019). The ESFT has an estimated incidence ranging from 2.5 to 3 cases per million individuals each year. This family of tumors represents approximately 3% of all childhood cancer (Jackson et al., 2016). These types of tumors are predominantly observed among pre-adolescents to young adults and is rarely diagnosed among infants and young children (De Ioris et al., 2013; Jackson et al., 2016; Van Den Berg, Dirksen, Ranft, & Jurgens, 2008; T. Wong et al., 2015). The 5-year survival rates for patients of this disease with metastatic tumors is 27%. However, among cases with localized ES, the 5-year survival rate is 85% (Jackson et al., 2016). ES staging is based on the size of the primary tumor, the extent of spread, metastases, and grade of tumor. ES tumors can be diagnosed in one of the following stages: (IA) the tumor is no more than 8cm across, is low grade, and has not spread to nearby lymph nodes or to distant parts of the body (ACS, 2018a), (IB) the tumor is either larger than 8cm or is in more than one place in the same bone, is low grade, and has not spread to nearby lymph nodes or distant parts of the body (ACS, 2018a), (IIA) the tumor is no more than 8cm across, is high grade, , and has not spread to nearby lymph nodes or to distant parts of the body (ACS, 2018a), (IIB) the tumor is larger than 8cm across, is high grade, and has not spread to nearby lymph nodes or to distant parts of the body (ACS, 2018a), (III) the tumor is in more than one place in the same bone, is high grade, and has not spread to nearby lymph nodes or to distant parts of the body (ACS, 2018a), (IVA) the tumor has spread only to the lungs and not to the lymph nodes or other parts of the body (ACS, 2018a), and (IVB) the tumor has spread to the nearby lymph nodes or the tumor has spread to distant parts of the body other than the lungs (ACS, 2018a).

Osteosarcoma

OS arise from mesenchymal cells and are characterized by the abnormal production of osteoids (Jackson et al., 2016). Primary OS is the most common bone malignancy among children and adolescents (Jackson et al., 2016; Jones & Barr, 2016). The majority of OS diagnoses occur during an individual's second decade of life (10-20 years) (Jones & Barr, 2016). The annual incidence of OS ranges from approximately 1-3 cases per million. The age-adjusted incidence rate is estimated to be 4.4 per million cases each year (Jackson et al., 2016). Secondary OS is associated with prior treatment with radiation or chemotherapy. This group represents approximately 1-3% of total OS cases (Henderson et al., 2012; Jackson et al., 2016; Thomas & Ballinger, 2015). The development of OS is correlated with the adolescent growth spurt. Therefore, OS occurs primarily among adolescents and young adults. OSs observed among children under 5 years old is exceedingly rare. Among the elderly, OS is associated with pre-existing Paget's disease, radiation, and/or chemotherapy (Jackson et al., 2016). OS are diagnosed in one of three stages: (I) OS is localized and low grade, (II) OS is localized and high grade, and (III) tumor has metastasized and is high grade (ACS, 2018d).

Rhabdomyosarcoma

Rhabdomyosarcomas (RMS) are tumors that arise from primary mesenchymal cells that show skeletal muscle differentiation (Dziuba, Kurzawa, Dopierała, Larque, & Januszkiewicz-Lewandowska, 2018; Koscielniak, Morgan, & Treuner, 2002; Malempati & Hawkins, 2012). These types of tumors are the third most common type of solid tumor and the most common sarcoma found in children (Dziuba et al., 2018; Leiner & Le Loarer, 2020; Yohe et al., 2019). Cases of RMS represent 5-10% of all childhood tumors and 3%

of all childhood cancers (Dziuba et al., 2018; Koscielniak et al., 2002; Malempati & Hawkins, 2012; Wachtel et al., 2006; Yohe et al., 2019). Each year in the United States there is an estimated 350 cases of RMS among children (Yohe et al., 2019). Among soft tissues sarcomas, RMS accounts for a larger proportion of childhood cases compared to adults, 45% and 19%, respectively. RMS is the most common soft tissue malignancy in the elderly. Approximately 90% of RMS cases occur in individuals under 25 years of age; 70% among children under 10 years old (Dziuba et al., 2018; Koscielniak et al., 2002; Malempati & Hawkins, 2012). The most common location on the body for RMS to develop is the head and neck region, accounting for 35-40% (Dziuba et al., 2018; Gurney, Severson, Davis, & Robison, 1995; Koscielniak et al., 2002; Malempati & Hawkins, 2012). RMS was previously categorized into two main types: alveolar and embryonal (Dziuba et al., 2018). However, in 2013 the WHO reclassified RMS into four types: embryonal RMS (PAX-fusion negative), alveolar RMS (PAX-fusion positive), pleomorphic RMS, and spindle cell/sclerosing RMS (Dziuba et al., 2018; Fletcher, Bridge, Hogendoorn, & Mertens, 2013; Yohe et al., 2019). Pleomorphic RMS occurs most often among adults, but are rarely diagnosed among children (Dziuba et al., 2018; Fletcher et al., 2013). Embryonal RMS (ERMS) are characterized by undeveloped, round cells with a hyperchromatic nucleus and basophilic cytoplasm. Alveolar RMS (ARMS) is characterized by poorly differentiated rhabdomyoblasts. Pleomorphic RMS (PRMS) can be identified by the presence of polymorphic, spindle, and multinucleated giant cells with acidophilic cytoplasm. Finally, spindle cell/sclerosing RMS is characterized by cells that are ribbon-shaped, can form arrangements of herring-bone pattern, or can be embedded in sclerotic submucosa (Dziuba et al., 2018). Pleomorphic RMS is only observed exclusively among

adults (Yohe et al., 2019). RMS is diagnosed in one of four stages: (I) tumor started in around the eye, head, neck, genital, urinary site, or bile ducts, (II) tumor started in bladder, prostate, arm, leg, parameningeal sites, or body part not include in stage I, (III) tumor started in bladder, prostate, arm, leg, parameningeal sites, or body part not included in stage I and the tumor is no more than 5cm across but has spread to nearby lymph nodes or the tumor is more than 5cm across but may not have spread to nearby lymph nodes, and (IV) tumor could have originated anywhere on the body, is of any size, and has spread to distant parts of the body (ACS, 2018f).

Non-Rhabdomyosarcoma

Childhood non-RMS soft tissue sarcomas (SRSTS) are a group of tumors that encompasses more than 50 different subtypes (Dasgupta & Rodeberg, 2016; Waxweiler et al., 2015). NRSTS arises from primitive mesenchymal tissue, similarly to RMS (Dasgupta & Rodeberg, 2016; Waxweiler et al., 2015). In the United States, these tumors account for 250-300 cases each year and make up approximately 50% of the soft tissue sarcomas identified among children and young adults (Dasgupta & Rodeberg, 2016; Martin-Broto, 2020). NRSTS represents approximately 8% of all childhood cancers. The Surveillance, Epidemiology, and End Results (SEER) data from 1975 to 2012 has identified NRSTS to be more common among adolescents and young adults compares to RMS (Dasgupta & Rodeberg, 2016; Ferrari et al., 2011). Furthermore, among individuals <18 years of age, NRSTS represents approximately 5% of cancers in the United States (Waxweiler et al., 2015). Synovial sarcoma is the most common subtype of NRSTS found in children (Martin-Broto, 2020).

Embryonal Tumors

Embryonal tumors are the most common malignant brain tumor found in children (McNeill, 2016). These tumors, also called "small blue cell tumors", are characterized by poorly differentiated and mitotically active cancers that arise from the developing embryonic nervous system (Drezner & Packer, 2016; Yachnis & Perry, 2018). Due to their mitotic activity, these tumors are generally very aggressive (Drezner & Packer, 2016). There are four main types of embryonal tumors: medulloblastomas, atypical teratoid/rhabdoid tumor (AT/RT), embryonal tumors with multilayer rosettes (ETMR), and CNS embryonal tumors (formally called PNETs (Kram et al., 2018; Yachnis & Perry, 2018). Medulloblastomas were previously discussed among central nervous system tumors. ATRTs primarily affects children; accounting for 1-2% of total childhood CNS tumors. Approximately two-thirds of ATRTs are located in the cerebellum (Kram et al., 2018; Rorke, Packer, & Biegel, 1996). ETMRs were first identified in 2009 and occurs in young children. These tumors can be categorized into three groups: embryonal tumors with abundant neuropil and true rosettes (ETANTR), ependymoblastoma (EBL), and medulloepithelioma (MEPL) (Korshunov et al., 2014; Kram et al., 2018; Spence et al., 2014). ETMRs are very aggressive and have a small median survival time following diagnosis (12 months). These tumors typically occur in children under 4 years of age (Kram et al., 2018).

Germ cell tumor

Intracranial germ cell tumors (IGCTs) is a very rare malignancy with 120-200 new cases each year in the United States (K. Wong, Abongwa, Chang, & Dhall, 2018). These tumors represent 3-5% of primary CNS tumors among children (K. Wong et al., 2018).

However, among adults these tumors are much less common (0.3-0.5%). IGCTs can be subdivided into two groups: germinomas and non-germinomatous germ cell tumors (NGGCTs) (K. Wong et al., 2018). NGGCTs are a heterogenous group of tumors that include embryonal carcinomas, endothermal sinus tumor, choriocarcinoma, mixed germ cell tumor, mature or immature teratoma, and teratoma with malignant transformation (K. Wong et al., 2018). Peak incidence for these tumors are in the second decade of life (10-20 years old), with 90% of cases occurring before 20 years old (K. Wong et al., 2018). Germinomas are most commonly diagnosed IGCT (65%) followed by teratomas (18%), endothermal sinus tumors (7%), embryonic carcinomas (5%), and choriocarcinomas (5%) (K. Wong et al., 2018).

Neuroblastoma

Neuroblastomas arise from embryonic nerve cells (Yachnis & Perry, 2018). The CNS neuroblastoma is a mitotically active tumor that is characterized by poorly differentiated neuroepithelial cells, neurophil-rich stroma, and groups of neurocytic cells (Yachnis & Perry, 2018). These tumors are commonly located in the abdomen and typically appear in children before they reach 2 years of age (Kleinsmith, 2006). Neuroblastomas are the third most frequent extracranial, neurogenic solid tumor identified in early childhood that is located within the peripheral sympathetic nervous system (Jezan, Salim, & Kutb, 2019; Kushner, Kramer, LaQuaglia, Modak, & Cheung, 2003). These tumors represent more than 7% of cancer cases and 15% of childhood cancer deaths among individuals under 15 years old (Jezan et al., 2019). Neuroblastomas originate from nerve tissues of the neck, chest, abdomen, or pelvis, and adrenal glands (Henderson et al., 2011; Jezan et al., 2019). The majority of neuroblastomas diagnosed are in children under 5 years

(90%). Cases among infants (under 1 year old) account for approximately 30% of these diagnoses (Colon & Chung, 2011; Jezan et al., 2019). Neuroblastomas can be diagnosed in one of the following stages: (I) cancer is still in area it originated from, is on one side of the body, lymph nodes outside of the tumor are free of cancer or surgery has removed all visible traces of the tumor; (IIA) cancer is still in area it originated from, is on one side of the body, lymph nodes outside of tumor contain neuroblastoma cells, cancer has not spread to lymph nodes of the other side of the body, or elsewhere, and may or may not have been removed completely by surgery; (IIB) cancer is on one side of the body, lymph nodes outside of tumor contain neuroblastoma cells, cancer has not spread to lymph nodes of the other side of the body or elsewhere, and may or may not have been removed completely by surgery; (III) cancer has not spread to distant parts of the body but either cancer cannot be removed completely by surgery and is on both sides of the body or has spread to nearby lymph nodes, or cancer is in the area where it originated and on one side of the body but has spread to nearby lymph nodes on other side of the body, or the cancer is located in the middle of the body, is growing away from its origin towards both sides, and cannot be removed completely by surgery; (IV) cancer has spread to distant sites (ACS, 2018c).

Wilms tumor

Wilms tumor (WT) , also called nephroblastoma, is a form of cancer that develops in the renal tissue and is typically diagnosed within the first five years of life (Zou et al., 2019). WT is the most common malignancy of the kidney and accounts for approximately 6% of cancers among children (Coorens et al., 2019; Gadd et al., 2017; Seminara et al., 2019). WT can arise in one or both kidneys, unilateral and bilateral, respectively. The majority of WT cases are unilateral (93-95%) and bilateral WTs which are very rare (3-

5%) (Seminara et al., 2019). The GBD estimates that worldwide the number of incident cases of childhood (0-14 years) renal tumors (predominantly Wilms tumor) was 13,794 in 2016 (Bhakta et al., 2019). The incidence of WT among children under 14 years old is 7.1 per million individuals each year (Coorens et al., 2019). Long-term cure rates among children are now exceeding 85% (Aldrink et al., 2019; Irtan, Ehrlich, & Pritchard-Jones, 2016). The International Society of Pediatric Oncology (SIOP) classifies WT based on histological type and risk: low risk (necrotic, blastomatosis), intermediate (epithelial, stromal, mixed, and regressive), and high (blastemal, clear cell, and rhabdoid) (Seminara et al., 2019). WT can be diagnosed in one of five stages: (I) the tumor is contain within one kidney and was removed completely by surgery, the tissue layer surrounding the kidney was not broken during surgery, the cancer has not grown into blood vessels in or next to the kidney, and the tumor was not biopsied before surgery to remove it; (II) the tumor has grown beyond the kidney into nearby fatty tissue or blood vessels in or nearby the kidney, but was completely removed by surgery, with no visible cancer left behind, nearby lymph nodes do not contain cancer, and the tumor was not biopsied before surgery; (III) tumor has not been removed completely, cancer remaining is limited to abdomen, and has either spread to lymph node in abdomen or pelvis but not too distant lymph nodes, or the tumor has grown into nearby vital structures so could not be removed, or deposit of tumor are found along inner lining of abdomen, or cancer cells are found at the edge of sample removed by surgery; (IV) the cancer has spread through the blood to organs away from the kidneys; (V) tumors are found in both kidneys at the time of diagnosis (ACS, 2018i).

Other cancers that rarely occur in children

Hepatoblastoma

Adult hepatoblastoma is a rare disease; to date, there have only been 64 reported in literature spanning from 1958 to 2019. Although adult hepatoblastoma is a rare malignancy, it is the most common childhood hepatic tumor (Al-jiffry, 2019; Celotti et al., 2016; Czauderna & Garnier, 2018; Sharma, Subbarao, & Saxena, 2017). This tumor typically arises in children before they turn 3 years old (Celotti et al., 2016). Hepatoblastomas can be made entirely of epithelial cells or a mixture of epithelial and mesenchymal cells. There are five types of hepatoblastomas: fetal HB, embryonal HB, pleomorphic epithelial HB, small cell undifferentiated HB, and cholangioblastic HB. Fetal hepatoblastomas arise from cells resembling fetal hepatoblasts seen in embryonal development. Embryonal HB is the most common type of HB and resembles the liver during 6 to 8 weeks of gestation. Pleomorphic epithelial HB is most common among individuals following intensive chemotherapy. Small cell undifferentiated HB is characterized by an aggressive biological course, leading to poor survival. Cholangioblastic HB is characterized by the differentiation of cholangiocytes forming ductal structures (Sharma et al., 2017). The introduction of chemotherapy dramatically improved the estimated overall 5-year survival rate within the last 30 years from 30% to 70% (Celotti et al., 2016; Czauderna & Garnier, 2018; Sharma et al., 2017).

Melanoma

Melanoma accounts for approximately 3% of all childhood cancers (Dean, Bucevska, Strahlendorf, & Verchere, 2017; Saiyed, Hamilton, & Austin, 2017). The majority of cases are diagnosed in patients >19 years old (98%), occurring very rarely

among children and adolescents (2%) (Dean et al., 2017; Tracy & Aldrink, 2016). In children, this form of cancer does not always follow ABCD (asymmetry, border, color, diameter) diagnostic criteria and has the potential to grow very aggressively (Dean et al., 2017). It is the second leading cause of cancer among individuals aged 15-29 years old and the deadliest form of skin cancer overall (Hamilton, 2016; Saiyed et al., 2017). Incidence varies by age, among 1-4 years old there are 1.1 per million each year and among 15-19 years old there is approximately a 10-fold increase (10.4 per million) (Hamilton, 2016; Saiyed et al., 2017). Childhood melanoma is believed to be biologically unique compared to adult melanoma (Tracy & Aldrink, 2016). A majority of studies suggest that the incidence of melanoma is decreasing; however, SEER estimates that the incidence of this malignancy has been decreased by 11.58% from 2000 to 2010. Melanoma can be classified into three main types: conventional melanoma (CM), melanoma arising in CNM, and spitzoid melanoma (Hamilton, 2016; Saiyed et al., 2017).

Retinoblastoma

Retinoblastoma (RB) is a small round blue-cell tumor. Therefore, it is histologically similar to neuroblastoma and medulloblastoma (Dimaras & Corson, 2019). It is the most common eye cancer found in children; representing approximately 3% of all childhood cancers (Dial et al., 2019; Dimaras & Corson, 2019; "What is Retinoblastoma?," 2018; Yamanaka, Hayano, & Takashima, 2019). RB arises in the developing retina from immature retinal cells, also called retinoblasts, that replace retina and intra-ocular tissues (Bhavsar, Subramanian, Sethuraman, & Krishnan, 2016; Dimaras & Corson, 2019; "What is Retinoblastoma?," 2018). RB is visible without using imaging technologies, making it unique among CNS tumors. This characteristic is attributed to the high level of calcification

of the tumor. Calcification results in the development of leukocoria, a white reflex visible through the pupil (Dimaras & Corson, 2019). The incidence of retinoblastomas is estimated to be 1 per 16,000 live births worldwide each year (Bhavsar et al., 2016; Dimaras & Corson, 2019; Yamanaka et al., 2019). SEER estimates that in the US the incidence of RB is 12.14 per million children ≤4 years old and 0.49 cases per million children between 5 and 9 years old. The incidence in the US has been consistent over the last four decades (Fernandes, Pollack, & Rabito, 2018). These tumors can affect one or both (bilateral) eyes and can also affect the pineal, parasellar, and suprasellar regions of the retina (trilateral retinoblastoma) (Dimaras & Corson, 2019). The overall 5-year survival rates for children diagnosed with retinoblastoma is over 96% in the US (Bhavsar et al., 2016; Brinkman et al., 2015; Fernandes et al., 2018). RB is diagnosed at one of the following stages: (IA) one tumor smaller than 4 disc diameters (DD) and at or behind equator, (IB) multiple tumors smaller than 4 DD and all at or behind the equator, (IIA) one tumor 4-10 DD and at or behind the equator, (IIB) one tumor larger than 10DD and behind the equator, (IVA) multiple tumors some larger than 10 DD, (IVB) any tumor extending toward the front of the eye to the front edge of the retina, (VA) tumors involving more than half of the retina, (VB) spread of tumors into the jelly like material filling the eye (ACS, 2018e).

2.3 Treatments for Childhood Cancer

Advances in the treatment of childhood cancers has dramatically improved the overall 5-years survival among these patients to over 80% (ACS, 2017a; S. M. Phillips et al., 2015; Robison & Hudson, 2014; Ward et al., 2014). However, a singular focus on curing cancer presents an incomplete view of childhood cancer survivorship (S. M. Phillips et al., 2015). In the United States, it is estimated that 1 out of every 750 individuals is a

survivor of childhood cancer and the population continues to grow with the total population reaching approximately 500,000 individuals (Robison & Hudson, 2014). The low specificity of treatment options for childhood cancer patients can result in late-effects due to the effects observed among normal and healthy tissues (S. M. Phillips et al., 2015). These effects encompass problems arising in multiple organ systems (Landier et al., 2018). This puts childhood cancer survivors at a higher risk of adverse health outcomes compared to individuals with no prior cancer history (Landier et al., 2018; Ward et al., 2014). These health outcomes include recurrence of primary cancers, subsequent malignancies, chronic diseases, health limitations, functional impairment (Ward et al., 2014), hospitalizations, premature frailty, psychologic distress, neurocognitive functioning, and reduced productivity (i.e., inability to work or a limitation of the type/amount of work) (Robison & Hudson, 2014). These late effects can negatively impact other aspects of normal life such as personal relationships, education, occupation, establishing independence, and negotiating family demands. In addition, childhood cancer survivors may suffer from multiple chronic conditions or limitations concurrently that require the need for comprehensive planning among healthcare professionals across multiple disciplines (S. M. Phillips et al., 2015). Healthcare professionals must conduct careful follow-up of childhood cancer survivors to detect and treat any late-effects that develop (ACS, 2017a).

Radiation

Radiation therapy among cancer patients is the use of ionized radiation to shrink tumors and kill cancer cells (ACS, 2017a; LLS, 2013). It can be used in two ways: from outside the body (external radiation) or from radioactive materials placed near the tumor site (internal radiation). However, the use of radiation can damage developing cells.

Typically, radiation therapy is used simultaneously with other forms of treatment (surgery and chemotherapy) (ACS, 2017a). This form of therapy has been essential to the success of treating many childhood malignancies (Green et al., 2013; Hudson et al., 2012). There are several factors that can influence the radiation-associated risk of adverse health outcomes among childhood cancer survivors. These factors include radiation source, cumulative dose, volume, and fractionation (dividing a dose of radiation to preserve normal tissue integrity), sex, and age at radiation exposure (Armstrong, Stovall, & Robison, 2010). However, fatigue is generally the most common side effect of radiation therapy, regardless of the area irradiated (COG, 2020). Organ-specific radiation will increase the risk of negative organ-specific outcomes in a dose-dependent manner (van Dijk et al., 2013). Adverse radiation-associated outcomes encompass cardiovascular (Van Der Pal et al., 2012), cerebrovascular (Bowers et al., 2006), gastrointestinal (Goldsby et al., 2011), endocrine (Merchant et al., 2011), reproductive (Green et al., 2010), pulmonary (Motosue et al., 2012), hepatic (Castellino et al., 2010), urinary tract (Baradaran-Ghahfarokhi, 2012), musculoskeletal (Merchant et al., 2004), neurologic, neurocognitive, and neurosensory deficiencies (Whelan et al., 2011). In addition, childhood cancer survivors are at an elevated risk for secondary malignancies such as skin, breast thyroid, bone, and brain cancers (Robison & Hudson, 2014).

Cranial radiation

Cranial irradiation therapy (CRT) to treat malignancies damages healthy tissue in the surrounding area. One of the most common effects of CRT is the development of cataracts (COG, 2020). Children diagnosed with ALL had a life expectancy of less than one year, but the introduction of CRT has increased the survival of these patients to

approximately 70% (Anderson, Godber, Smibert, Weiskop, & Ekert, 2000). Due to the late effects of this form of therapy, CRT is not as common in practice as it once was. Research has shown that children who received CRT in combination with chemotherapy can experience cognitive, educational and behavioral difficulties (Fujii et al., 2020). Childhood cancer survivors who were treated with cranial radiation have an elevated risk of several adverse effects, including secondary malignancies such tumors of the CNS, head, and neck (Fujii et al., 2020; Ward et al., 2014). Children irradiated may suffer sexual developmental deficits including reaching puberty at an unusual age (LLS, 2013). Children that received cranial radiation may have a higher risk of dental problems. These individuals should have frequent dental visits (every 6 months). Cranial radiation can cause hearing problems (ASCO, 2019b). These individuals are at higher risk of vision and eye problems (ASCO, 2019b).

Abdominal radiation

Abdominal radiation can cause abdominal discomfort, cramping, difficulty eating, fatigue, nausea/vomiting, reproductive deficits, and skin changes (COG, 2020). In girls, adnominal radiation can cause fertility problems such as premature ovarian failure and premature menopause (LLS, 2013). In addition, radiation to the upper abdomen can contribute to adverse cardiac effects (ASCO, 2019b). Radiation in this region of the body can promote digestive system problems (ASCO, 2019b).

Chest radiation

Chest radiation can result in chest pain/discomfort, cough, difficulty swallowing, fatigue, shortness of break and skin changes (radiation dermatitis) (COG, 2020). In addition, these individuals can suffer from lung damage, hypothyroidism, hyperthyroidism,

or second primary malignancies (breast, thyroid, or bone cancer) (LLS, 2013). Radiation to this part of the body can increase the risk of adverse cardiac effects including leaky heart valves, coronary artery disease, weakness of heart muscle and cardiac dysrhythmia (ASCO, 2019b). Women that were treated with chest radiation therapy for HL have an increased risk of developing breast cancer. Current guidelines recommend having an MRI annually along with mammographic screen for women that received chest radiation (Ward et al., 2014). Radiation in this region of the body can also promote digestive system problems (ASCO, 2019b).

Pelvic radiation

Pelvic radiation can cause fertility problems in men and women. Effects seen in testes and ovaries will depend on location, dosage, and age of treatment (LLS, 2013). These effects include cramping, fatigue, diarrhea, painful and frequent urination, and skin changes (COG, 2020) Radiation can also cause digestive system problems (ASCO, 2019b).

Chemotherapy

Chemotherapy is the use of drugs to treat cancer (ACS, 2017a). Chemotherapeutic agents also are essential in the treatment of childhood cancers (Robison & Hudson, 2014). The type of chemotherapeutic agent used can result in a broad range of late effects (Robison & Hudson, 2014). Children are growing at the time of diagnosis and treatment; their cells are dividing more rapidly compared to adults. Chemotherapy can damage cells and prevent them from developing properly (ACS, 2017a). Certain chemotherapeutic agents, such as alkylating agents and epipodophyllotoxins, have a dose-response relationship with the development of subsequent neoplasms (Turcotte et al., 2017). These agents include alkylating agents, anthracycline antibiotics, glucocorticoids, antimetabolites,

corticosteroids, epipodophyllotoxins and alkaloids. Risk of adverse health outcomes from chemotherapeutic agents is amplified by dose, sex, and age at treatment (Robison & Hudson, 2014). Chemotherapy given to a child whose adult teeth have not formed are at an elevated risk of dental problems including abnormal tooth development, gum disease and cavities. These individuals should have frequent dental visits (every 6 months) (ASCO, 2019b).

Alkylating Agents

Alkylating agents are highly reactive organic molecules that trigger DNA damage and are used in treating cancer (Kleinsmith, 2006). These agents have an observed association with cardiovascular and pulmonary problems, risk for secondary cancers, low testosterone levels and sperm counts, premature ovarian failure (POF), or premature menopause (LLS, 2013). The use of alkylating drugs in combination with radiation therapy significantly raises the risk for fertility problems (LLS, 2013). Common types of alkylating drugs are cyclophosphamide, procarbazine, nitrogen mustard, ifosfamide, carmustine, busulfan, carboplatin and cisplatin (LLS, 2013). Cisplatin and carboplatin are associated with hearing problems. It is recommended that children who received these drugs consult with an audiologist at least once following their treatment (ASCO, 2019b).

Anthracyclines

Patients who were treated with anthracyclines are at an elevated risk for adverse cardiac effects (e.g., chronic heart failure, heart muscle injury) (Robison & Hudson, 2014; Ward et al., 2014). Damage occurring to heart muscle is related to the dose of anthracycline. Common types of anthracyclines are doxorubicin, daunorubicin, idarubicin, and mitoxantrone (ASCO, 2019b; LLS, 2013). Childhood cancer survivors who received

anthracyclines should have regular follow-up to monitor these conditions, especially in regards to cardiovascular health (ASCO, 2019b).

Corticosteroids

Corticosteroids are commonly used to treat childhood leukemia and lymphoma. Corticosteroids have been shown to be associated with the development of osteoporosis and cataracts. These medications have been used to treat childhood leukemia and lymphoma (LLS, 2013). Administration of corticosteroids have been shown to induce ischemia, upregulate apoptosis of osteoblasts and osteocytes, and prolong osteoclast lifespans (Hyakuna et al., 2014). In addition, high doses of corticosteroids may increase the risk of avascular necrosis of the hip and subsequent hip replacement. Common drugs in this category include dexamethasone and prednisone (LLS, 2013). Treatment with dexamethasone and prednisone are associated with growth, development, and hormone problems. These corticosteroids have a direct effect on bone formation and can result in low bone mineral density or osteoporosis (ASCO, 2019b). This disease causes weak bones and increases the risk of serious injury (ASCO, 2019b). However, most children will regain their bone density following discontinuation of these medications but remain at higher risk of vision and eye problems (ASCO, 2019b). There are two main types of corticosteroids: glucocorticoids and mineralocorticoids. Glucocorticoid use in patients may promote adverse health effects that include weight gain, osteoporosis, osteonecrosis, cataracts, hyperglycemia, diabetes, CVD, and infection (Gensler, 2013).

Antimetabolites

Antimetabolites are molecules made to resemble naturally occurring substances that are involved in cellular metabolism and used for cancer therapy (Kleinsmith, 2006).

Furthermore, these molecules disrupt metabolic pathways that occur in cancer (Kleinsmith, 2006). Antimetabolites prevent the division of cancerous cells. Methotrexate is a type of antimetabolite that is associated with learning and memory problems, unusual bone formation, low bone mineral density, and osteoporosis (ASCO, 2019b).

Surgery

Surgery involves the removal of the tumor and, perhaps, some additional surrounding healthy tissue (ASCO, 2019a). This form of treatment is generally used along with other forms of treatment to ensure the elimination of cancer cells (ACS, 2017a). Surgical procedures used to treat childhood malignancies may be minor or major and can negatively impact the long-term health status and quality of life among childhood cancer survivors (Robison & Hudson, 2014). In severe cases, it may be required to remove part or all of an organ, or limb (ACS, 2017a). Amputations and limb-sparing procedures can negatively impact the physical function, mobility, and independence (Robison & Hudson, 2014). The goal when surgery is performed is to remove as much of the tumor as possible while avoiding healthy tissue (ASCO, 2019a; Ward et al., 2014). In some cases, surgical removal of the tumor is not possible without damaging healthy tissue (Ward et al., 2014). There are many additional reasons for surgery including to diagnose cancer, visualize the location of the cancer, determine if the cancer has spread or is affecting the function of surrounding organs, restore the body's appearance, to relieve side-effects, so some combination of these (ASCO, 2019c).

Brain Surgery

Brain surgery can be performed for the following reasons: to obtain a biopsy and determine the type of tumor, removal or destruction of the tumor, and to help treat

symptoms or complications from the tumor (ACS, 2018g). Surgical treatment for CNS tumors is dependent on the location, size, histology, grade, and other prognostic factors (ASCO, 2019a; Ward et al., 2014). Generally, a neurosurgeon will attempt to remove or destroy as much of the tumor as possible without damaging normal brain or nerve function. Surgical treatment alone or combined with radiation therapy may be effective in controlling or curing slower-growing tumors such as low-grade astrocytomas, ependymomas, gangliogliomas, and meningiomas. Tumors growing into nearby healthy tissue cannot be treated through surgery alone. However, surgery to remove as much of the tumor as possible can improve the efficacy of radiation or chemotherapy (ACS, 2018g). Craniotomy is the most common surgery performed for the removal of brain tumors and is the surgical procedure used to make an opening in the skull (ACS, 2018g). Patients who present with hydrocephalus (accumulation of CSF in the brain) are at an elevated risk for late-onset epilepsy, motor, sensory, and behavioral deficits (Janss, Mazewski, & Patterson, 2019).

Thoracotomy

Thoracotomy is a surgical procedure that makes an incision to open the chest (MSKCC, 2018; NCI, 2020a). The location of the incision is in the back and below the shoulder blade; depending on which side needs treatment. This procedure is performed when surgery is required on or near the lung (MSKCC, 2018). It typically requires a large incision, rib retraction, and possible division of the latissimus dorsi (Malkan, Loh, Fernandez-Pineda, & Sandoval, 2014). Children rarely receive thoracotomies in comparison to adults because the incidence of diseases requiring this procedure is much lower in this group (Malkan et al., 2014). Differences in anatomic and physiologic features

put children at higher risk for postoperative complication compared to adults (Malkan et al., 2014).

Amputation

Amputations among children present unique challenges to normal growth and development (Loucas, Brand, Bedoya, Muriel, & Wiener, 2017; Nowicki & Sandieson, 2002). Losing a limb permanently changes a child's ability to move independently, touch, play, and interact with their surrounding environment compared to children who did not undergo an amputation. Furthermore, childhood is a time of increased influence from peers, increased importance on body image. Children have been shown to prefer other children without handicaps compared to those who are physically handicapped (Loucas et al., 2017; Nowicki & Sandieson, 2002). Amputations commonly occur in response to Ewing sarcoma, osteosarcomas, and some soft tissue sarcomas (Atala & Carter, 1992; Loucas et al., 2017).

Limb sparing

Limb sparing surgery is a procedure used to remove a tumor in a limb without amputation. The bone and tissue surrounding the tumor site also may be removed. Occasionally, implants may be used to replace the section of the limb that was surgically removed. Limb sparing is used to treat bone and soft tissue malignancies with the goal of saving the use and appearance of the limb (NCI, 2020b).

Other Surgical Procedures: Laparotomy and Splenectomy

Laparotomy is surgery used to stage ovarian cancer, HL, and neuroblastomas. This procedure entails making a large cut down the middle of an individual's abdomen. Subsequent collection of tissue sample (biopsies) is then performed. This surgical

procedure is used to treat ovarian cancer in women and girls (Falcetta et al., 2016). Splenectomy is a surgical procedure to remove one's spleen. Splenectomies are used to treat specific forms of cancer such as CML, HL, NHL. Spleen removal can increase an individual's lifelong risk of subsequent infection (MayoClinic, 2018).

Other Systemic Treatments

Systemic therapy is the use of medications to treat and destroy malignant cells. Medications are administered into the bloodstream to reach cancer cells throughout distal parts of the body. Common forms of systemic therapy includes intravenous (IV) tube inserted directly into a vein or giving the patient a pill orally (ASCO, 2019a).

Statins

Statins (3-hydroxy-3-methylglutaryl-CoA) were originally developed to reduce blood cholesterol (Joungyoun Kim et al., 2020) and are used for the primary prevention of CVD (Cai, Zhang, Wang, Luo, & Zhou, 2015; A. Smith, Murphy, Bennett, & Barron, 2017). Among individuals with preexisting history of CVD, statins are used for secondary prevention, lowering lipid levels, and promoting short-term anti-inflammatory effects. In addition, statins can be used to modulate immune responses and inhibit oxidative stress (Joungyoun Kim et al., 2020). However, statin use may only be effective among high-risk individuals (A. Smith et al., 2017). Recent studies suggest that statins may be effective in preventing cancer and its progression due to changes in cell signaling that promote apoptosis and inhibition of angiogenesis (Cai et al., 2015; Joungyoun Kim et al., 2020). These include liver, colorectal, bladder, gynecologic, and lung cancers. Pravastatin, a commonly used statin, have be observed to significantly inhibit colon carcinogenesis (Cai et al., 2015; Joungyoun Kim et al., 2020).

2.4 Risk Factors for Chronic Diseases Following Childhood Cancer

Diet

Among childhood cancer survivors, >30% consume calories that exceed the recommended individual levels of intake (J. Cohen et al., 2012; Landy et al., 2013; Teixeira, Maia-Lemos, & Pisani, 2018). In addition, childhood cancer survivors consume diets that promote inadequate lipid levels in the blood (Teixeira et al., 2018). Saturated fatty acids and trans fatty acids promote chronic inflammation but some polyunsaturated fatty acids have been observed to cause a reduction in both inflammation and the risk of chronic disease (Teixeira et al., 2018). Childhood cancer survivors are consistently observed to consume diets that are low in fruit, vegetable, and calcium intake and high in fat intake (Barnea, Raghunathan, Friedman, & Tonorezos, 2015; Stolley et al., 2010; F. F. Zhang et al., 2018; F. F. Zhang & Parsons, 2015). Dietary habits in combination with PA have a strong effect on metabolism and cardiovascular health (Barnea et al., 2015). In 2007, a study assessed dietary intake of adult childhood cancer survivors (ALL) using the National Cancer Institute Diet History Questionnaire (NCI-DHQ) and observed poor adherence to the recommended dietary guidelines (Robien, Ness, Klesges, Baker, & Gurney, 2008). Another study by Berden and colleagues, assessed adherence to dietary recommendations using the Dietary Approaches to Stop Hypertension (DASH) diet, the World Cancer Research Fund/American Institute for Cancer Research Cancer Prevention guide, and the US Department of Agriculture Food guide. Childhood cancer survivors were observed to have low adherence to these recommended guidelines, specifically childhood cancer survivors had low fiber intake and high intake of sodium, sugar, and meat (Berdan, Tangney, Scala, & Stolley, 2014). In 2013, a study assessed the adherence among

childhood cancer survivors of ALL to the Mediterranean diet pattern and found that adherence was associated with a significant reduction in the risk of MetS and obesity. Interestingly, small changes in adherence was seen to significantly impact metabolism. For example, for everyone point increase in diet score a 31% decrease in risk for MetS was observed (Tonorezos et al., 2013). Inadequate diets among childhood cancer survivors also can result in changes to the gut microbiota and produce metabolic abnormalities such as obesity and insulin resistance (Barnea et al., 2015; Burcelin, Garidou, & Pomié, 2012; Vrieze et al., 2014). High-fat diets can promote enhanced calorie digestion by the microbiota as well as alterations to the immune system. This commonly results in a state of chronic inflammation with elevated levels of IL-6, IL-1, and TNF-α (Barnea et al., 2015; Burcelin et al., 2012; Vrieze et al., 2014). In addition, diet plays an important role in mental health among children and adolescents. Unhealthy dietary patterns have been shown to consistently promote poorer mental health in this group (Mayr et al., 2018; Ramallal et al., 2017; Tabung et al., 2015). However, there is very little evidence among children and adolescents that suggests a healthy diet is effective in improving mental health (O'Neil et al., 2014).

Metabolic Health

Obesity is one of the most common and significant late effects among childhood cancer survivors (Barnea et al., 2015). Long-term survivors of childhood ALL who received either total body irradiation (TBI) or abdominal radiation are at highest risk for obesity (Barnea et al., 2015; Tonorezos et al., 2015). ALL survivors that are women and have a history of CRT have been observed with higher levels of fasting insulin and glucose, were more insulin resistant based on the Homeostasis Model for Assessment of Insulin

Resistance (HOMA-IR) (Barnea et al., 2015). Many childhood cancer patients are obese at the time of their diagnosis. This puts them at higher risk of obesity later in life (Barnea et al., 2015). In addition, empirical evidence suggests that weight gain occurs among childhood cancer patients during therapy, regardless of gender, age, or weight at the time of diagnosis (Barnea et al., 2015).

Metabolic Syndrome (MetS) is a characterized by a number of metabolic abnormalities, these include hyperinsulinemia, obesity, insulin resistance, dyslipidemia, glucose intolerance, and hypertension (Barnea et al., 2015; Scott et al., 2015). Childhood cancer survivors of specific primary cancers (i.e. lymphomas, neuroblastomas, acute lymphoblastic leukemia, and testicular tumors) have been observed to display clinical features of MetS (Gurney et al., 2006; K. E. Hoffman et al., 2008; Link et al., 2004; Nuver et al., 2005; Scott et al., 2015). Among healthy children, the prevalence of MetS can range from 3.6% to 4.8% but can exceed 30% in children who are overweight and obese. Among childhood cancer survivors, cancer therapies such as chemotherapy and radiation, have been discovered to activate certain pathways that have the potential of leading to hormone deficiencies, inflammatory mediators, lipid metabolism, changes in insulin activity, and adipokines (Scott et al., 2015). In addition, MetS is found at high levels in cancer survivors of testicular cancer, brain cancer, ALL, lymphoma, neuroblastomas, and Wilms tumor (K. E. Hoffman et al., 2008). These survivors generally suffer from dyslipidemia, hyperglycemia, hypertension, and obesity; putting these individuals at higher risk for diabetes and CVD (K. E. Hoffman et al., 2008). In a study by Phillips and colleagues, there was a higher prevalence of MetS among individuals who consumed diets high in inflammatory potential compared to those who consumed diets with low inflammatory

potential. Indicating that diets rich in pro-inflammatory food items can significantly contribute to the risk of MetS (C. M. Phillips et al., 2018a). However, pro-inflammatory diets as a risk for MetS has not yet been studied among childhood cancer survivors.

Anxiety and Depression

Psychological distress are significant in certain subgroups of childhood cancer survivors. Specifically, survivors of leukemia, neuroblastomas, bone tumors, and lymphomas have been observed to have an increased risk of depression and anxiety (Mitchell, Ferguson, Gill, Paul, & Symonds, 2013; Zeltzer et al., 2009). In addition, childhood cancer survivors across certain treatment subgroups are at an increased risk of depression and anxiety (Zeltzer et al., 2009). Survivors who received chemotherapy have shown an association between treatment and psychological distress (Zeltzer et al., 2009). However, some treatment subgroups experience lower levels of psychological distress. For example, childhood cancer survivors that undergo surgical procedures leading to amputation report lower levels of anxiety and depression (Zeltzer et al., 2009). Research indicates that diet is important predictor of depression and anxiety (Akbaraly et al., 2009; Jacka et al., 2010; Lai et al., 2014; O'Neil et al., 2014; Panagos et al., 2016; C. M. Phillips et al., 2019; Sen et al., 2018; Shivappa, Hebert, & Rashidkhani, 2017; Shivappa, Hebert, et al., 2018). Diets consistent with recommendations are associated with better mental health outcome among adults (Akbaraly et al., 2009; Jacka et al., 2010; Lai et al., 2014; O'Neil et al., 2014). In addition, poor diets increase the risk of depression and anxiety (O'Neil et al., 2014). High levels of inflammation promotes chronic conditions that are known to elevate the risk for adverse mental health outcomes, such as CVD, MetS, diabetes, asthma, multiple sclerosis (MS)) (Kiecolt-Glaser et al., 2015). Studies on children

also have demonstrated this relationship between inflammation and depression (JW Kim, Szigethy, Melhem, Saghafi, & Brent, 2014).

Cardiovascular Disease (CVD)

Cardiovascular disease (CVD) is now recognized as a leading contributor of morbidity and mortality among childhood cancer survivors (Chow et al., 2015). CVD among this population is present at earlier ages compared to individuals from the general population (Chidwick et al., 2018; Mulrooney et al., 2016). Potential cardiotoxic effects of radiotherapy and systemic therapy contribute to the elevated risk seen in childhood cancer survivors (Chidwick et al., 2018). Survivors are a significant risk of suffering from cardiomyopathy that leads to eventual congestive heart failure (CHF). Doses of chest radiotherapy is an important risk factor leading to CHF (Chow et al., 2015). Female childhood cancer survivors are at a higher risk for poor cardiovascular outcomes, including congestive heart failure, compared to male survivors (Mertens et al., 2008). Despite the recognition of the dangers of CVD among childhood cancer survivors, little research has focused on quantifying the risk in this population (Barac et al., 2015). Survivors of childhood ALL are at risk for late occurring cardiovascular disease, including hypertension and hyperlipidemia (Barnea et al., 2015). ALL survivors that are women and have a history of CRT have a higher probability of developing two or more cardiovascular risk factors compared to the general population. In addition, a healthy diet and regular PA reduces the risk for cardiovascular morbidity and mortality (Barnea et al., 2015).

2.5 Conclusions

Childhood cancer survivors are at an elevated risk of several adverse health effects (Hudson, Ness, Gurney, Mulrooney, Chemiatilly, et al., 2013; Landier et al., 2018). These

problems are attributed to the physical, emotional, and psychological tolls experienced by survivors during multimodal therapy (Kunin-Batson et al., 2016; Loucas et al., 2017; Tai et al., 2012; Walter, Nixon, Davey, Downie, & Horne, 2015). Following treatment for their malignancies, childhood cancer survivors adopt unhealthy lifestyle behaviors that can exacerbate these effects (Lown et al., 2016). Diet, specifically, can be an important regulator of the physiologic factors that attribute to this added risk (F. F. Zhang et al., 2016). Furthermore, an inadequate diet can promote chronic inflammation (Cavicchia et al., 2009; Shivappa et al., 2014). Chronic inflammation can inhibit the ability of the body to resolve future health events appropriately resulting in an increase of the severity of these events (Bergmans & Malecki, 2017; Faugere et al., 2017; C. M. Phillips et al., 2018a; Shivappa, Godos, et al., 2018; Welsh, Grassia, Botha, Sattar, & Maffia, 2017).

CHAPTER 3

METHODS

3.1 Study Population

The SJLIFE study began in 2007 and was created with the intention of studying adults who were previously treated childhood cancer at SJCRH. SJLIFE uses a retrospective cohort design with prospective follow-up of childhood cancer survivors treated at SJCRH between 1962 and 2012 (Howell et al., 2020). Eligibility criteria for participants in SJLIFE cohort include (1) diagnosis of childhood cancer that was treated at SJCRH and (2) survival of childhood cancer for >5 years (Howell et al., 2020; Hudson et al., 2011). A total of 8,192 participants were recruited into the SJLIFE study. There were a total of 4,418 males (53.9%) and 3,774 females (46.1%). The race distribution in this cohort was 79.3% White, 16.9% Black, and 3.8% other. The majority of potential participants were survivors of ALL (27.2%), CNS tumors (17.5%), and HL (9.0%) (Howell et al., 2020). A total of 5,756 individuals elected to participate in SJLIFE. Eligibility into this study is limited to SJCRH alumni who have the necessary macro and micronutrient data needed to compute the DII. There are three possible levels participation for participants in SJLIFE: (1) comprehensive evaluation at SJCRH, (2) limited local evaluation for survivors that decline returning to SJCRH, or (3) completion of health surveys either by mail or phone for alumni that decline returning to SJCRH or receiving local evaluation (Hudson et al., 2011). Medical record abstraction included all

chemotherapy, surgical procedures, radiation treatment (energy source, dose, and fields), and health events (Hudson et al., 2011). SJLIFE participants complete several health questionnaires ranging in various health topics. A total of 883 items are assessed ranging from: (1) health history and current health status, (2) social and demographic factors, (3) health behaviors, (4) psychosocial functioning, and (5) psychosexual health (Hudson et al., 2011). Every participant in the SJLIFE cohort undergoes a periodic risk assessment based on their age at diagnosis, primary diagnosis, and therapies received based on the Children's Oncology Group Long-Term Follow-Up Guidelines for Survivors of Childhood Adolescent and Young Adult Cancer (COG Guidelines) (Hudson et al., 2011; Landier et al., 2004). Most childhood cancer survivors in the SJLIFE cohort will undergo scheduled medical assessments every 2-5 years to monitor the impact of aging on health status and organ function (Hudson et al., 2011).

3.2 Exposure

Dietary Intake

Dietary data were collected using the self-administered 2005 Block Food Frequency questionnaire for approximately 110 food items and nutrients consumed over the past year (F. F. Zhang et al., 2018). Completed FFQs were processed by Block Dietary Data Systems to estimate nutrient intake based on a food list from National Health and Nutrition Examination Survey (NHANES) and food composition values for nutrients from USDA Food and Nutrient Database for Dietary Studies (F. F. Zhang et al., 2016).

The DII® is a tool that was developed in order to measure the inflammatory potential of a person's diet. This tool quantifies the individual's dietary intake on a continuous scale ranging from maximally anti-inflammatory (approx. -9) to maximally

pro-inflammatory (approx. +9) based on a refined scoring algorithm of peer-reviewed articles identified from 1950-2010 (Shivappa et al., 2014). Across several populations variability in total energy intake was observed, leading to the development of the Energy-adjusted- DII (E-DII). The E-DII was created to adjust for caloric content of the diet consumed using the 'nutrient density model' (i.e., amount per 1,000 kilocalories (kcal) (Mazidi et al., 2018). The DII and E-DII are scored similarly and scaled identically; so, the scores are comparable across studies (Hébert, Shivappa, Wirth, Hussey, & Hurley, 2019). The DII and E-DII have since been construct validated 28 times against several inflammatory biomarkers in various populations (Bodén et al., 2017; Julia et al., 2017; Kizil et al., 2016; Kotemori et al., 2018; Mayr et al., 2018; Na et al., 2018; C. M. Phillips et al., 2018a; Sen et al., 2015; Shivappa, Hebert, Marcos, et al., 2017; Shivappa, Hébert, et al., 2015; Shivappa, Steck, et al., 2015; Shivappa, Wirth, et al., 2017, 2018; Tabung et al., 2015; Vahid et al., 2018; Vahid, Shivappa, Hekmatdoost, et al., 2017; M. D. Wirth, Shivappa, Davis, et al., 2017). Information on dietary intake was assessed using a food frequency methodology (Hudson et al., 2011). DII scores were calculated for survivors and controls using macro and micronutrient data from the Block FFQ. The DII is a continuous measure where a higher score is considered more pro-inflammatory (Shivappa et al., 2014).

3.3 Outcomes

Markers of Inflammation

C-reactive Protein (CRP) is a protein synthesized by the body's liver. A CRP level greater than 10 milligrams per liter (mg/L) indicates an inflammatory reaction (Dhingra et al., 2007). Blood sample was drawn to assess high sensitivity CRP levels from SJLIFE participants. Blood draws were performed at the same age as the FFQ was filled out by

participants A blood analysis was performed to carry out CRP high sensitivity. A CRP level of ≤3 mg/L is indicative of no inflammation. Individuals with low-grade inflammation have a CRP level >3 mg/L (Osimo, Baxter, Lewis, Jones, & Khandaker, 2019; Perry, Oltean, Jones, & Khandaker, 2020). A CRP level greater than 10 milligrams per liter (mg/L) indicates an acute inflammatory reaction from a potential infection among cancer survivors (Dhingra et al., 2007; Perry et al., 2020; Villaseñor et al., 2014); these participants were removed from the validation analysis (n=35).

Markers of Metabolic Health

A fasting laboratory battery (blood counts, insulin level, glycosylated hemoglobin, lipid panel, and metabolic panel) was performed to estimate insulin and glycosylated hemoglobin levels (Mulrooney et al., 2016). Hemoglobin A1c is an assay used to diagnose diabetes and to detect individuals at increased risk for the disease. Normal levels of hemoglobin A1C is <5.7%, prediabetes is 5.7-6.4%, and diabetes is ≥ 6.5% (Lorenzo et al., 2010). Fasting Insulin is classified as a normal level if it is between 2.1 and 30 microunits/ml. Fasting glucose was measures from plasma samples following an overnight fast (Williams et al., 2020). Fasting Glucose is an elevated level of fasting blood sugar is greater than 100 milligrams per deciliter (mg/dL) (Prasad & Patil, 2019). Treatment with glucose lowering medications is also indicative of insulin resistance or diabetes. The Resistance Calculation (HOMA-IR) has a cutoff for insulin resistance based on the following equation: Insulin (µm/ml) x Glucose (mmol/L) ÷ 22.5 (Assume Fasting prior to 2010) (J. Chen et al., 2004). This cutoff categorizes normal as <2.86 and insulin resistance as ≥ 2.86 (J. Chen et al., 2004). Waist circumference was estimated to the nearest tenth centimeter with a Gulick spring tape measure (Wogksch et al., 2018). Waist

Circumference (WC) is the distance around the waist just above the hipbones at the level of an individual's naval measured after exhalation (Men: WC >40 inches (102 cm); Women: WC>35 inches (88cm)) (Wilcox, 2005). A fasting lipid panel was carried out to estimate triglyceride and HDL levels among SJLIFE participants (Hudson, Ness, Gurney, Mulrooney, Chemaitilly, et al., 2013). Triglycerides are a type of fat (lipid) found in the bloodstream. Normal triglyceride levels are less than 150 milligrams per deciliter (mg/dL), borderline high levels are between 150 and 199 mg/dL, and high levels are between 200 and 400 mg/dL (Clinic, 2018). High density lipoprotein (HDL) is a lipoprotein that removes cholesterol from the bloodstream. Elevated risk from low levels of HDL are below 60 mg/dL (Men: <40 mg/dL; Women: <50 mg/dL) (Wilcox, 2005).

Mental Health

Depression is a common but detrimental mood disorder. Symptoms of the disorder can adversely affect how you think, feel, and perform daily activities (such as sleeping and working). Depression status can be determined through the use of self-report measures that assess the severity and whether individuals do or do not have depressive symptoms. The Brief Symptom Inventory-18 (BSI-18) is an 18-item self-report symptom checklist that assesses somatic, anxiety, and depressive symptoms. The validity of the BSI-18 is supported through its 3-factor structure (i.e., anxiety, depression, and somatization) that was based on adult survivors of childhood cancer (Grassi, Caruso, Mitchell, Sabato, & Nanni, 2018; Recklitis et al., 2006), breast cancer (Galdón et al., 2008; Grassi et al., 2018), and pancreatic cancer patients (Clark, Loscalzo, Trask, Zabora, & Philip, 2010; Grassi et al., 2018). Each item is rated on a 5-point scale according to the how much the symptom has bothered an individual in the prior week. The depression assessment is made up of a 6-

item subscale (Zeltzer et al., 2009). Anxiety is a mood disorder that is characterized by a display of excessive worry, most days for at least 6 months regarding social interactions, personal health, work, and daily activities. Anxiety status can be determined through the use of self-report measures that assess items related to the disorder. Raw BSI-18 scores are converted into t-scores. These t-scores were then dichotomized with a clinically significant cut point of ≥ 63 as being sufficient to classify an individual as having psychological distress from the specific disorder (anxiety or depression) (Recklitis, Blackmon, & Chang, 2017; Recklitis et al., 2006; Zeltzer et al., 2009). T-scores were analyzed as both continuous and binary response variables for SJLIFE participants.

Cardiovascular Diseases (CVD)

CVD outcomes were graded and classified using the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE v4.03) (Hudson et al., 2017). All CVD outcomes were defined as Grade 2 or above. Hypertension is a disorder characterized by an increase in systolic and diastolic blood pressure (SBP and DBP, respectively). . Hypertension (grade 2) was defined as having systolic blood pressure (SBP) ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg and taking medication (Bhakta et al., 2016). Hyperlipidemia is a disorder characterized by an elevated concentration of lipids in blood. The normal range is less than or equal to 200 dL for total cholesterol, less than or equal to 150 mg/dL for triglycerides, less than or equal to 130 mg/dL for LDL, and less than or equal to 40 mg/dL for HDL. Hyperlipidemia is graded as follows: Grade 1- 150mg/dL to 300 mg/dL; Grade 2- >300 mg/dL to 500 mg/dL (treatment with one lipid lowering agent); Grade 3- >500 mg/dL to 1000 mg/dL (treatment with <=2 lipid lowering agents); Grade 4- >1000 mg/dL (Life-threatening); and Grade 5- Death (Hudson et al.,

2017). For this study, Hyperlipidemia was defined based on total cholesterol, triglycerides, LDL, and HDL among participants (hypertriglyceridemia >300 mg/dL and/or hypercholesterolemia ≥300 mg/dL) and/or taking medication. Screening for hyperlipidemia was done through the use of a fasting lipid panel (Hudson, Ness, Gurney, Mulrooney, Chemiatilly, et al., 2013). Cardiomyopathy is characterized by the heart's inability to pump blood at an adequate volume to meet metabolic requirements of bodily tissue, or only having the ability to do so only through elevating filling pressure. Cardiomyopathy is graded as follows: Grade 1- Not applicable; Grade 2- Resting EF < 50-40%; 10 - 19% absolute drop from baseline; Grade 3- Resting EF 39-20%; >20% absolute drop from baseline; medication indicated or initiated; Grade 4- Resting EF<20%; refractory or poorly controlled heart failure due to drop in ejection fraction; on medical management; intervention such as ventricular assist device, intravenous vasopressor support, or heart transplant indicated; and Grade 5- Death (Hudson et al., 2017). For this study, Cardiomyopathy was defined as a systolic ejection fraction <50% on an echocardiogram (Mulrooney et al., 2016). Coronary artery disease (CAD) is characterized by blockage of one or more arteries that supply blood to the heart (includes myocardial infarction). CAD is graded as follows: Grade 1- Asymptomatic, clinical or diagnostic observations only, intervention not indicated; Grade 2- Mild symptoms and cardiac enzymes minimally abnormal and no evidence of ischemic ECG changes; Grade 3- Severe symptoms, cardiac enzymes abnormal, hemodynamically stable, ECG changes consistent with infarction (Q waves); Grade 4- Life-threatening consequences, hemodynamically unstable (CABG or angioplasty); and Grade 5- Death (Hudson et al., 2017). CAD was defined as having abnormal cardiac enzymes and no evidence of ischemic changes on

electrocardiogram (ECG) (Mulrooney et al., 2016). Cardiac dysrhythmia is an abnormal rhythm detected through the use of an electrocardiogram which will require treatment. Dysrhythmia is graded as follows: Grade 1- Asymptomatic, intervention not indicated; Grade 2- Non-urgent medical intervention indicated; Grade 3- Symptomatic and incompletely controlled medically, or controlled with device, or ablation; Grade 4- Life-threatening consequences; urgent intervention indicated; and Grade 5- Death (Hudson et al., 2017). For this study, cardiac dysrhythmia was defined by the detection of a rhythm abnormality on an ECG (Hudson, Ness, Gurney, Mulrooney, Chemiatilly, et al., 2013). Cerebrovascular accidents (CVAs) are disorders that can be identified by a decrease or absence of blood supply to the brain resulting in neurological damage which will require treatment (includes stroke). Stroke is graded as follows: Grade 1- Asymptomatic or mild neurologic deficit, radiographic findings only; Grade 2- Moderate neurologic deficit; Grade 3- Severe neurologic deficit; Grade 4- Life-threatening consequences, urgent intervention indicated; and Grade 5- Death (Hudson et al., 2017). CVAs (including stroke) are considered moderate events. Other information on CVAs were identified through the use of the International Classification of Diseases (ICD-9), 9th revisions (ICD-9: 430-434, 436, 437, 438, and 444); ICD-10 codes were also used (diagnosis codes beginning with I63) (Chow et al., 2018; Hsieh, Hsieh, Tsai, Wang, & Sung, 2020).

3.4 Other Covariates

Other variables to consider and to adjust for include demographic factors, lifestyle factors, and the type of treatment received. Demographic factors include age, sex, race, and education. Age at first visit to SJCRH was used. Race was categorized into 3 groups: White, Black, and other. Education was categorized into 4 groups: 1-12 grade but did not graduate,

high school (HS) diploma or GED, training after HS or some college, and college graduate. Lifestyle factors include PA, smoking status, and alcohol intake. Adequate levels of PA were defined by the Center for Disease Control and Prevention (CDC) and the American College of Sport Medicine. Adequate PA requires an accumulation of 30 minutes or more of moderate activity for at least 5 days per week or vigorous activity for at least 3 days per week that results in a health benefit (Martin, Morrow, Jackson, & Dunn, 2000). PA status will be dichotomized as having 'met recommendations' or 'did not meet recommendations. Smoking status was also dichotomized as being an 'ever smoker' or 'never smoker'. An ever smoker is defined as a person who has smoked a minimum of 100 cigarettes throughout their lifetime, a never smoker is defined as a person who smoked less than 100 cigarettes in their lifetime (Cataldo, Jahan, & Pongquan, 2012). Treatments include radiation (cranial, abdominal, chest, and pelvic), chemotherapy (alkylating agents, anthracyclines, glucocorticoids, and antimetabolites), surgery (brain, thoracotomy, laparotomy, splenectomy, amputation, and limb sparing), and medications (statins). All treatment variables were dichotomized into two groups (Yes/No).

3.5 Specific Aims

Specific Aim 1. Investigate the cross-sectional associations between DII scores and markers of inflammation and metabolic health among childhood cancer survivors and controls.

Hypothesis: A pro-inflammatory diet (higher DII score) is associated with an increased odds of elevated hs-CRP. Also, we hypothesize that a pro-inflammatory diet is associated with an increased odds of metabolic health outcomes (hemoglobin A1C, fasting glucose,

fasting insulin, insulin resistance (HOMA-IR), waist circumference, HDL, triglycerides, and MetS).

Specific Aim 2. Identify the cross-sectional associations between DII scores and adverse mental health outcomes (depression and anxiety) among childhood cancer survivors and controls.

Hypothesis: A pro-inflammatory diet is associated with an increased odds of anxiety and depression.

Specific Aim 3. Identify the cross-sectional associations between DII scores and cardiovascular disease (CVD) among childhood cancer survivors and controls.

Hypothesis: A pro-inflammatory diet is associated with an increased odds of CVD outcomes (hypertension, hyperlipidemia, cardiomyopathy, coronary artery disease (CAD), cardiac dysrhythmia, and cerebrovascular accidents).

3.6 Statistical Analysis

The statistical software SAS 9.4 (SAS Institute, Cary, NC, USA) was used for all analyses. Use of the DII or E-DII will be determined using model fit statistics, the Akaike Information Criterion (AIC). The DII/E-DII was analyzed as a continuous variable and categorized into quartiles. ANOVA or Kruskal Wallis tests were used to estimate the means and standard deviations (SD) or medians and interquartile ranges (IQR) for continuous variables across DII/E-DII quartiles. Chi-square tests were performed to estimate the frequencies and percentages for binary and categorical variables across DII/E-DII quartiles. Multiple Imputation will be used to address missing covariate data in this study. First, plausible values (imputations) will be generated for missing values. Second, data will be

analyzed in a pre-determined number of imputations (e.g., 100 times). Third, all generated imputations will be combined into a single estimate.

Specific Aim 1. Investigate the cross-sectional associations between DII scores and markers of inflammation and metabolic health among childhood cancer survivors and controls.

To investigate the potential association between DII/E-DII scores and CRP, linear and logistic regressions models were performed. Odds Ratios and 95% Confidence intervals will be generated using logistic regression. Multivariable models assessing the association between DII/E-DII scores were adjusted for age, sex, race, education, BMI, smoker status, heavy drinking, meeting PA recommendations, any radiation, and any chemotherapy.

To investigate the potential associations between DII/E-DII scores and metabolic outcomes (hemoglobin A1C, fasting insulin, fasting glucose, insulin resistance, waist circumference, triglyceride levels, HDL, and MetS), logistic regression models were performed, and Odds Ratios and 95% Confidence Intervals were generated. Multivariable models assessing the association between DII/E-DII scores and metabolic outcomes were adjusted for age, sex, race, education, BMI, smoker status, heavy drinking, meeting PA recommendations, and any radiation therapy.

Specific Aim 2. Identify the cross-sectional associations between DII scores and adverse mental health outcomes (depression and anxiety) among childhood cancer survivors and controls.

To investigate the association between DII/E-DII scores and anxiety and depressive symptoms, both linear and logistic regression models were used. Anxiety and depressive symptoms t-scores were analyzed as both a continuous and dichotomous response variable.

Multivariable models assessing the associations between the DII/E-DII and mental health outcomes were adjusted for age, race, education, BMI, smoker status, heavy drinking, meeting physical activity recommendations, cranial radiation, use of alkylating agents, and the study population (survivor/control).

Specific Aim 3. Identify the cross-sectional associations between DII scores and cardiovascular disease (CVD) among childhood cancer survivors and controls.

To investigate the association between DII/E-DII scores and CVD outcomes, logistic regression models were used in the analysis. Multivariable models were carried out adjusted for covariates that were specific to each outcome. All multivariable models were adjusted for age, sex, race, education, BMI, smoker status, heavy drinking, and meeting PA recommendations. Multivariable models for hypertension were in addition adjusted for alkylating agents, antimetabolites, and chest radiation. Multivariable models for hyperlipidemia were also adjusted for alkylating agents, and chest radiation. Multivariable models for cardiomyopathy were also adjusted for anthracyclines, and chest radiation. CAD was also adjusted for hypertension status, and hyperlipidemia status. Multivariable models for cardiac dysrhythmia were also adjusted for hypertension status, and chest radiation. Finally, multivariable models for CVA were also adjusted for cranial radiation.

CHAPTER 4

VALIDATION OF THE ENERGY-ADJUSTED DIETARY INFLAMMATORY INDEX (E-DII) WITH C-REACTIVE PROTEIN (CRP) AND ASSOCIATIONS WITH METABOLIC HEALTH AMONG CHILDHOOD CANCER SURVIVORS: THE ST. JUDE LIFETIME COHORT STUDY (SJLIFE)

Abstract

Introduction: With significant improvements in diagnosis and treatment over the past 7 decades, the 5-year survival for childhood cancer exceeds 84% in the United States. These survivors have elevated incidence of adverse health effects later in life. Diet-associated inflammation may be an important component in the development of adverse metabolic health outcomes among childhood cancer survivors.

Methods: We studied 4,520 childhood cancer survivors and controls from St. Jude Lifetime Cohort Study (SJLIFE) to evaluate the effect of diet-associated inflammation on inflammatory and metabolic biomarkers using the Energy-adjusted Dietary Inflammatory Index (E-DII^{TM}), which were calculated based on food frequency questionnaires. The E-DII will be assessed as a continuous predictor and categorized into quartiles (quartile 1 is the most anti-inflammatory and quartile 4 is the most pro-inflammatory). We examined associations between the E-DII and hs-CRP, hemoglobin A1C, HOMA-IR, fasting glucose,

fasting insulin, waist circumference, high-density lipoproteins, triglycerides, and metabolic syndrome. We used multivariable linear and logistic regression models to assess the strength of the associations between the E-DII and these outcomes. Finally, multivariable analyses will be stratified by sex.

Results: The average age (mean ± std) was 30.9 ± 8.8 years. A pro-inflammatory diet was significantly associated with insulin resistance (HOMA-IR) ($OR_{Quartile\ 4vs1}$ = 1.28, 95% CI: [1.13, 1.44]) and HDL cholesterol ($OR_{Quartile\ 4vs1,}$ = 1.23, 95 CI: [1.09, 1.38]). Among men, a pro-inflammatory diet was associated with insulin resistance ($OR_{Quartile\ 4vs1,}$ = 2.06, 95% CI: [1.48, 2.86]) and elevated triglyceride levels (150-199 mg/dL) ($OR_{Quartile\ 4vs1,}$ = 2.00, 95 CI: [1.22, 3.29]). Among women, a pro-inflammatory diet was associated with insulin resistance ($OR_{Quartile\ 4vs1,}$ = 1.51, 95% CI: [1.08, 2.10]), and HDL cholesterol ($OR_{Quartile\ 4vs1,}$ = 1.64, 95 CI: [1.21, 2.24]). Diet-associated inflammation was not observed to be significantly associated with hs-CRP in this population.

Discussion: The DII was observed to be significantly associated with certain metabolic health outcomes among childhood cancer survivors. As the population of childhood cancer survivors continues to increase, research needs to be focused on understanding the relationship between childhood cancer, subsequent inflammatory potential of diet, survivorship, metabolic outcomes, and identify means through which individuals can modify their risk of future adverse outcomes.

Keywords: Inflammation, childhood cancer survivors, metabolic health

4.1 Introduction

The second leading cause of death for children 5-14 years old in the United States (US) is childhood cancer (Ward et al., 2014). However, mortality has steadily declined

each year since 1975, resulting in a dramatic decrease of over 50% (Ward et al., 2014). Today, it is estimated that there are over half a million childhood cancer survivors living in the US (Armstrong et al., 2016; Y. Chen et al., 2020; Robison & Hudson, 2014). Survivors remain at an elevated lifetime risk for recurrence of their primary cancers, development of neoplasms, functional impairments, and adverse chronic health conditions (Armstrong et al., 2016; Cardous-Ubbink et al., 2004; Dowling et al., 2010; M. C. Hoffman et al., 2013; S. M. Phillips et al., 2015; Pui et al., 2003; Reulen et al., 2010; Robison & Hudson, 2014). Poor metabolic health has become an increasingly recognized problem observed among childhood cancer survivors (Gunn, Emilsson, Gabriel, Maguire, & Steinbeck, 2016). For example, childhood cancer survivors have been reported to have twice the risk of developing type 2 diabetes compared to non-survivors (Gunn et al., 2016).

Generally, poor metabolic health, such as metabolic syndrome (MetS) and diabetes, increases the risk of cardiovascular disease (CVD) among survivors (Danielle Novetsky Friedman, Tonorezos, & Cohen, 2019; Scott et al., 2015). CVD is the second leading cause of mortality among this population, making prevention of poor metabolic health paramount in this group of survivors (Danielle Novetsky Friedman et al., 2019). MetS is a term comprised of several metabolic abnormalities including obesity, insulin resistance, elevated insulin levels, and abnormal lipid levels (Scott et al., 2015). Chronic inflammation stemming from prolonged exposure to chronic stressors can promote the onset of metabolic syndrome (Sokol et al., 2016).

Lifestyle factors, such as diet, play a key role in the regulation of metabolic abnormalities among childhood cancer survivors (Gunn et al., 2016; Scott et al., 2015; F. F. Zhang et al., 2019). Additionally, lifestyle factors, such as diet, are now recognized as

important regulators of the inflammatory response (F. F. Zhang & Parsons, 2015). Inadequate dietary intake can lead to a state of chronic inflammation through the inhibition of anti-inflammatory cytokines (Khan et al., 2018; Ramallal et al., 2017; Saita et al., 2014). A state of chronic inflammation can lead to a wide array of adverse metabolic outcomes such as MetS, obesity, hyperinsulinemia, insulin resistance, dyslipidemia, and glucose intolerance (Chow et al., 2015; Khan et al., 2018; Mertens et al., 2001; Ramallal et al., 2017; Saita et al., 2014; Scott et al., 2015). Among childhood cancer survivors, a higher risk of metabolic syndrome has been observed to be associated with elevated levels of pro-inflammatory cytokines (IL-2, IL-10, IL-17a, and hs-CRP) (Ariffin et al., 2017). The link between diet-associated inflammation and metabolic syndrome has been established in several studies using the Dietary Inflammatory Index (DII®) (Mazidi et al., 2018; Neufcourt et al., 2015; C. M. Phillips et al., 2018a).

The DII® is a tool that was originally developed to accurately estimate the inflammatory potential of an individual's dietary intake (Cavicchia et al., 2009; Shivappa et al., 2014). This tool uniquely quantifies an individual's dietary intake on scale that ranges between maximally anti-inflammatory to maximally pro-inflammatory. The DII has been validated against inflammation markers in 33 different populations (Bodén et al., 2017; Julia et al., 2017; Kizil et al., 2016; Kotemori et al., 2018; Mayr et al., 2018; Na et al., 2018; C. M. Phillips et al., 2018a; Sen et al., 2015; Shivappa, Hebert, Marcos, et al., 2017; Shivappa, Hébert, et al., 2015; Shivappa, Steck, et al., 2015; Shivappa, Wirth, et al., 2017, 2018; Tabung et al., 2015; Vahid et al., 2018; Vahid, Shivappa, Hekmatdoost, et al., 2017; M. D. Wirth, Shivappa, Davis, et al., 2017). We predict that a pro-inflammatory diet is

positively associated with elevated hs-CRP levels and an elevated risk of metabolic health outcomes among childhood cancer survivors and controls.

4.2 Methods

Study Population

The St. Jude Lifetime Cohort Study (SJLIFE) began in 2007 at the St. Jude Children's Research Hospital (SJCRH), an NCI (National Cancer Institute)-designated Comprehensive Cancer Center. This cancer center is dedicated exclusively to the treatment of childhood cancer and provides comprehensive medical services for both children and adolescents with malignancies (Hudson et al., 2011). Initially, the study was intended for adults treated for a childhood malignancy who had survived at least 10 years following their cancer diagnosis (Howell et al., 2020). Eventually, the cohort expanded to include individuals of all ages who had survived for at least 5 years following their cancer diagnosis (Howell et al., 2020). SJLIFE uses a retrospective cohort study design and implements prospective follow-up of patients who were diagnosed and treated at SJCRH from 1962-2012. SJLIFE has recruited age-, sex-, and race-frequency matched controls without a history of childhood malignancies. Eligibility criteria specific to this analysis is contingent on the availability of the necessary macro- and micronutrient intakes of childhood cancer survivors. There are three available levels of participation available to childhood cancer survivors in SJLIFE: (1) comprehensive evaluation at SJCRH, (2) limited local evaluation for survivors that decline returning to SJCRH, or (3) completion of health surveys either by mail or phone for alumni that decline returning to SJCRH or receiving local evaluation. Comprehensive treatment (radiation, chemotherapy, and surgery) and prior health event information was obtained through medical record abstraction (Hudson et al., 2011).

Dietary Assessment

SJLIFE participants complete five questionnaires that query (1) demographics, health history and health status; (2) health habits; (3) behavioral health; (4) psychosexual health; and (5) dietary intake the self-administered Block 2005 Food Frequency Questionnaires (FFQ) (Hudson et al., 2011). The FFQ assessed the usual dietary intake of approximately 110 food items and nutrients consumed during the past 12 months (F. F. Zhang et al., 2018). The DII was used to quantify the inflammatory potential of each individual's diet in the SJLIFE cohort based on their food intake. Completed FFQs were processed by Block Dietary Data Systems which estimates the nutrient intake of SJLIFE participants on the basis of food-composition values for nutrients from the USDA Food and Nutrient Database for Dietary Studies and a food list from National Health and Nutrition Examination Survey (NHANES) (F. F. Zhang et al., 2016).

Dietary Inflammatory Index (DII®) and Energy-Adjusted DII (E-DII™)

The DII is a tool developed to quantify the inflammatory potential of an individual's diet (Shivappa et al., 2014). The DII measures a person's nutritional intake on a continuous scale than ranges from maximally anti-inflammatory to maximally pro-inflammatory. DII scores are based on a refined scoring algorithm of peer-reviewed articles identified from 1950-2010 that assessed the associations between dietary macro- and micro-nutrients and inflammatory markers that include: IL-1β, IL-4, IL-6, IL-10, TNF-α, and C-Reactive Protein (CRP) (Shivappa et al., 2014). Articles were assigned three possible values based on the significant changes in pro-inflammatory markers (IL-β, IL-6, TNF- α, or CRP) and/or significant changes in anti-inflammatory marker (IL-4, IL-10). A score of '+1' denotes a significant increase in pro-inflammatory markers or a significant decrease in anti-

inflammatory markers. A score of '-1' denotes a significant increase in anti-inflammatory markers or a significant decrease in pro-inflammatory markers. A score of '0' denotes no significant changes in inflammatory markers. Articles were weighted according to their study design and corresponding causal inference in order to calculate pro- and anti-inflammatory fractions. Next, the 'article effect score" was calculated by (1) dividing the weighted articles by the total number of weighted articles and (2) subtracting anti-inflammatory fractions from pro-inflammatory fractions. A composite database was then created that was representative of a wide range of dietary intakes across the globe. Dietary information collected and the composite database are both used to calculate z-scores. Z-scores are then converted to centered-percentiles to avoid 'right skewing'. Centered-percentiles are then multiplied by the respective 'overall food parameter-specific inflammatory effect score' to estimate the 'food parameter-specific DII score'. These parameter-specific scores are then added together to calculate the 'overall DII score'. Conducting research using the DII has led to the realization that individuals tend to eat more of everything as their energy intake increases. In addition, 'heathy eater' (nutrient dense and energy-sparse diet) and 'unhealthy eater' (energy-dense and nutrient sparse diet) effects have been observed to produce negative correlations between energy density and nutrient density (Darmon, Darmon, Maillot, & Drewnowski, 2005; Drewnowski & Fulgoni, 2014; Hébert et al., 2019). These observations led to the development of the Energy-Adjusted DII (E-DII^{TM}) which ultimately calculates the DII using nutrient densities per 1,000 calories consumed. The DII and E-DII are scored similarly and scaled identically; so, the scores are comparable across studies (Hébert et al., 2019). The E-DII showed better model fits compared to the DII based on Akaike Information Criteria (AIC) (Portet, 2020).

Calculation of E-DII scores among SJLIFE participants was based on a total of 27 macro- and micronutrients assessed based on FFQ responses (Shivappa et al., 2014). A higher E-DII score is indicative of a more pro-inflammatory diet.

High Sensitivity C-Reactive Protein (hs-CRP)

C-reactive Protein (CRP) is a protein synthesized by the body's liver. This biomarker provides the ability to assess systemic inflammation among individuals in the SJLIFE cohort. Blood samples were drawn to assess high sensitivity CRP levels from 416 SJLIFE participants. Blood draws were performed at the same age as the FFQ was filled out by participants. A blood analysis was performed to carry out CRP high sensitivity at SJCRH via immunoturbidimetry. A hs-CRP level of ≤3 mg/L is indicative of no inflammation. Individuals with low-grade inflammation have a CRP level >3 mg/L (Osimo et al., 2019; Perry et al., 2020). A CRP level greater than 10 milligrams per liter (mg/L) indicates an acute inflammatory reaction from a potential infection among cancer survivors (Dhingra et al., 2007; Perry et al., 2020; Villaseñor et al., 2014); these participants were removed from the validation analysis (n=35).

Markers of Metabolic Health

A fasting laboratory battery (blood counts, metabolic panel, insulin level, glycosylated hemoglobin and lipid panel) was performed to estimate insulin and glycosylated hemoglobin levels following an overnight fast (Mulrooney et al., 2016). Hemoglobin A1C is an assay that estimates the average blood sugar levels. It is used to diagnose type 2 diabetes and to detect individuals at increased risk for the disease (Lorenzo et al., 2010). Normal levels of hemoglobin A1C are <5.7%, prediabetes is 5.7-6.4%, and diabetes is ≥ 6.5% (Lorenzo et al., 2010). However, the oral glucose tolerance test (OGTT)

remains the gold standard for diagnosing diabetes (Brar, 2019; Jesudason, Dunstan, Leong, & Wittert, 2003). Fasting Insulin is classified as a normal level if it is between 2.1 and 30 microunits/ml. Fasting glucose was measured from plasma samples following an overnight fast (Williams et al., 2020). Fasting Glucose is at an elevated level of fasting blood sugar if it exceeds 100 milligrams per deciliter (mg/dL) (Prasad & Patil, 2019). The Homeostasis Model of Assessment of Insulin Resistance (HOMA-IR) is determined through using the formula: fasting serum insulin (U/ml) x fasting plasma glucose (mmol/L) / 22.5 (J. Chen et al., 2004). HOMA-IR cutoff for insulin resistance was set at <2.86 and ≥2.86 since all participants in this study were 18 years old and older (Endukuru, Gaur, Yerrabelli, Sahoo, & Vairappan, 2020; Danielle N. Friedman et al., 2018). Waist circumference was estimated to the nearest tenth centimeter with a Gulick spring tape measure (Wogksch et al., 2018). Waist Circumference (WC) is the distance around the waist just above the hipbones at the level of an individual's naval measured after exhalation (Men: WC >40 inches (102 cm); Women: WC >35 inches (88cm)) (Wilcox, 2005). Triglycerides are a type of fat (lipid) found in the bloodstream. A fasting lipid panel was carried out to estimate triglyceride and HDL levels among SJLIFE participants (Hudson, Ness, Gurney, Mulrooney, Chemaitilly, et al., 2013). Normal triglyceride levels are less than 150 milligrams per deciliter (mg/dL), borderline high levels are between 150 and 199 mg/dL, and high levels are between 200 and 400 mg/dL (Clinic, 2018). High density lipoprotein (HDL) is a lipoprotein that removes cholesterol from the bloodstream. Low levels of HDL are below 60 mg/dL (Men: <40 mg/dL; Women: <50 mg/dL) (Wilcox, 2005). Finally, MetS is defined by the Adult Treatment Panel III (ATP III) of the National Cholesterol Advisory Panel as requiring three of the following: abdominal obesity, fasting

glucose ≥ 110 and < 126 mg/dL, blood pressure ≥ 130/80 mmHg, triglycerides > 150 mg/dL, HDL cholesterol <40 mg/DL (men) and <50 mg/dL (women) (Wilcox, 2005).

Covariates

Variables to consider and to adjust for include demographic factors, and lifestyle factors. Demographic factors include age, gender, race, and education. Age at the time of their first visit was used. 'Race' was split into 3 categories: White, Black, or other. Education was divided into 4 categories: 1^{st}-12^{th} grade but did not graduate, high school (HS) diploma or GED, training after HS or some college, and college graduate. Lifestyle factors include physical activity (PA), smoking status, and alcohol intake. Performing adequate PA was the determined based on the definition by the Center or Disease Control and Prevention (CDC) and the American College of Sports Medicine. This requires individuals to accumulate 150-300 minutes of moderate PA a week or vigorous PA for 75-150 minutes per week in order to achieve a health benefit (Martin et al., 2000; Piercy et al., 2018). An ever smoker is defined as a person who has smoked a minimum of 100 cigarettes throughout their lifetime, a never smoker is defined as a person who smoked less than 100 cigarettes in their lifetime (Cataldo et al., 2012). Heavy alcohol use is defined as consuming more than 4 drinks in a day for men and more than 3 drinks in a day for women (Alcoholism, n.d.). Body Mass Index (BMI) is a simple calculation based on an individual's weight in kilograms divided by their height in meters squared (kg/m^2). Individuals are considered underweight if they have a BMI less than 18 kg/m^2, normal weight if their BMI is between 18-25 kg/m^2, overweight if their BMI is between 25 and 29.9 kg/m^2, and obese if their BMI is above 30 kg/m^2 (Kramer et al., 2016). Underweight and normal weight individuals were combined due to the small number of underweight

individuals in the study. Treatments include radiation (cranial, abdominal, chest, and pelvic), and chemotherapy (alkylating agents, anthracyclines, glucocorticoids, and antimetabolites). Radiation therapy and chemotherapy received during treatment for their diagnosis was determined for each participant (yes/no) (Howell et al., 2020).

Covariates were selected for the multivariable models using a method called "disjunctive causal criterion". This method controls for covariates that are associated with the exposure, the outcome, or both. This method does not require full knowledge of the causal diagram for each model (Vanderweele, 2021). This was used since limited knowledge is available of the associations between treatment measures for childhood cancers and diet-associated inflammation.

Statistical Analysis

The statistical software SAS 9.4 (SAS Institute, Cary, NC, USA) was used for all analyses. The E-DII was analyzed as a continuous variable and categorized into quartiles (quartile 1 being the most anti-inflammatory and quartile 4 being the most pro-inflammatory). ANOVA or Kruskal-Wallis were used to estimate the means and standard deviations (SD) or medians and interquartile ranges (IQRs) for continuous variables across E-DII quartiles on basis of normality. Chi-square tests were performed to estimate frequencies and percentages for categorical variables across E-DII quartiles. In addition, ANOVA was used to estimate the means and standard deviations (SD) of parameter intake among SJLIFE participants. Multiple Imputation (MI) was used to address missing data in this study (i.e., education, smoking status, and heavy drinking). The first step involved generating plausible values (imputations) for missing values. The second step involved analyzing the data through a pre-determined number of imputations (100). The third step

involved combining all generated imputations into a single estimate. Specifically, fully conditional specification (FCS) approach to imputation was used. Furthermore, the FCS approach allows for imputation of binary and categorical variables. In addition, FCS is a more flexible method of imputation compared to other methods, such as Multivariate normal imputation (MVNI) (Lee & Carlin, 2010; van Buuren, 2007).

To investigate the relationship between CRP and the DII, linear and logistic models were performed. Multivariable models assessing the relationship between E-DII scores and CRP levels were adjusted for age, sex, race, education, BMI, smoker status, heavy drinking, meeting PA recommendations, any radiation, and any chemotherapy. In addition, logistic regression was used to investigate the relationship between E-DII scores and metabolic outcomes (hemoglobin A1C, fasting glucose, fasting insulin, insulin resistance, waist circumference, triglyceride levels, HDL, and MetS). Multivariable models assessing the relationship between the E-DII and metabolic outcomes were adjusted for age, sex, race, education, BMI, smoker status, heavy drinking, meeting physical activity recommendations, any radiation therapy, and study population (survivor or control).

4.3 Results

A total of 4,520 members of the SJLIFE cohort with evaluable data, specifically, 588 community controls and 3,932 survivors that were diagnosed for a pediatric malignancy between 1962 and 2012, were included in this study (Hudson et al., 2011). Descriptive statistics of the SJLIFE participants in this study are presented across quartiles of the EDII in Table 4-1. The mean age was 30.7 ± 8.8 years old in the study population. E-DII scores ranged from -5.84 to 4.57 among participants. Overall, individuals in the highest quartile (quartile 4) of EDII scores had an average age of 29.5 ± 8.4 years old.

Individuals in this quartile were more likely to be survivors, men, younger, Black, less educated, ever smokers, heavy drinkers, and physically inactive (based on CDC recommendations) compared to individuals in quartile 1.

SJLIFE participants with the highest energy intake were more likely to be in the highest quartile. Individuals in the first quartile had the highest intakes of magnesium, vitamin A, vitamin B6, vitamin C, vitamin E, dietary fiber, beta carotene, and isoflavones. Individuals in the fourth quartile had the highest intakes of carbohydrates, total fat, saturated fat, monounsaturated fatty acids (MUFAs), polyunsaturated fatty acids (PUFA), trans fat, and cholesterol. In addition, individuals in the fourth quartile also had the lowest intakes of magnesium, vitamin A, riboflavin, vitamin B6, vitamin C, vitamin D, vitamin E, dietary fiber, beta-carotene, and isoflavones (Table 4-2).

Inflammatory marker (hs-CRP)

The age-adjusted, and multivariable linear models showed nonsignificant decreases (p-value > 0.05) in CRP levels for each unit increase in the E-DII. Similarly, the age-adjusted, and multivariable logistic models with the dichotomous CRP response variable showed that the log odds of CRP had a nonsignificant decrease for every one unit increase in E-DII scores. Finally, CRP analyzed as a categorical variable also showed nonsignificant decreases in the log odds for every unit increase of the E-DII comparing individuals with CRP levels 1-3 mg/L to individuals with CRP <1 mg/L and individuals with >3 mg/L to individuals with CRP < 1mg/L (Table 4-3).

CRP as a continuous variable showed nonsignificant decrease in CRP comparing quartile 4 to quartile 1 in the multivariable model. The logistic regression with CRP as a binary response showed a nonsignificant decrease in the odds of elevated CRP levels (≤

3mg/L) comparing quartile 4 to quartile 1. In the multivariable model with CRP as a categorical response variable, a significant decrease was observed in CRP > 3 mg/L comparing quartile 4 to quartile 1 (Table 4-4).

For CRP as a binary response variable, individuals in quartile 4 had nonsignificant negative associations between CRP >3 mg/L and the E-DII across all three models. For CRP as a categorical response variable, the odds of having CRP between 1-3 mg/L showed nonsignificant negative associations in all 3 models comparing quartile 4 to quartile 1. The odds of having CRP >3 mg/L showed a significant negative association in the multivariable model comparing quartile 4 to quartile 1 ($OR_{Multivariable} = 0.47$, 95% CI: [0.25, 0.87]).

Metabolic Outcomes

Hemoglobin A1C. Results from the multivariable logistic regression assessing the odds of hemoglobin A1C as a dichotomous response variable (≥5.7%) shows nonsignificant associations comparing quartiles 4 quartile 1. Interestingly, a significant positive association was observed comparing quartile 3 to quartile 1 ($OR_{Quartile\ 3vs1} = 1.22$, 95% CI: [1.06, 1.40]). Hemoglobin A1C was also analyzed as a categorical variable. The logistic regression assessing the odds of hemoglobin A1C between 5.7% and 6.4% showed a nonsignificant negative association comparing individuals in quartile 4 to individuals in quartile 1. The logistic regression assessing the odds of hemoglobin A1C ≥ 6.5% showed a significant negative association comparing quartiles 4 to quartile 1 ($OR_{Quartile\ 4vs1} = 0.67$, 95% CI: [0.48, 0.94]) (Table 4-6). The logistic regression models stratified by sex showed nonsignificant positive associations between hemoglobin A1C and E-DII scores comparing men quartile 4 to men quartile 1. In contrast, a nonsignificant negative association was observed between hemoglobin A1C as a binary response variable and E-DII scores

comparing women in quartile 4 to women in quartile 1. For hemoglobin A1C as a categorical response variable, a nonsignificant positive association was seen between hemoglobin A1C (5.7%-6.4%) and EDII scores comparing women in quartile 4 to 1. However, a significant negative association was observed for hemoglobin A1C (≥6.5) and E-DII scores comparing women in quartile 4 to quartile 1 ($OR_{Quartile\ 4vs1}$ = 0.30, 95% CI: [0.11, 0.84]) (Table 4-7).

HOMA-IR. Results from the multivariable logistic regression assessing the odds of HOMA-IR ≥ 2.86 showed a significant positive association comparing quartiles 4 to quartile 1 ($OR_{Quartile\ 4vs1}$ = 1.28, 95% CI: [1.13, 1.44]) (Table 4-6). Among males, those in E-DII quartile 4 experience an increased odds insulin resistance compared to those in quartile 1 ($OR_{Quartile\ 4vs1,}$ = 2.06, 95% CI: [1.48, 2.86]). This was consistent when comparing men in quartiles 2 and 3 to men in quartile 1. Among females, those in E-DII quartile 4 experienced an increased odds of insulin resistance compared to those in quartile 1 ($OR_{Quartile\ 4vs1,}$ = 1.51, 95% CI: [1.08, 2.10]). This was consistent in quartiles 2 and 3 as well (Table 4-7).

Fasting Glucose. Results from the multivariable logistic regression assessing the odds of elevated fasting glucose as a dichotomized response variable(≥100 mg/dL), shows a nonsignificant negative association comparing E-DII quartiles 4 compared to quartile 1. Similarly, results from the logistic regression assessing the odds of elevated fasting glucose as a categorical response variable, showed a nonsignificant positive association between elevated fasting glucose 100-125 mg/dL and E-DII scores comparing quartile 4 to quartile 1. In contrast, results from the logistic regression assessing odds of elevated fasting glucose ≥126 mg/dL) showed a nonsignificant negative association with E-DII scores comparing

quartile 4 to quartile 1 (Table 4-6). Among men, nonsignificant positive associations were observed between elevated fasting glucose levels and E-DII scores comparing quartile 4 to quartile 1. Among women, fasting glucose as a binary response variable showed nonsignificant negative association with E-DII scores comparing quartile 4 to quartile 1. Interestingly, when analyzing fasting glucose as a categorical response variable women in quartile 4 were seen to have a significantly lower odds of elevated fasting glucose ≥126 mg/dL compared to women in quartile 1 ($OR_{Quartile\ 4vs1,} = 0.29$, 95% CI: [0.10, 0.84]) (Table 4-7).

Insulin. The multivariable logistic regression assessing the odds of low insulin levels showed a nonsignificant negative association with E-DII scores comparing quartile 4 to quartile 1. Elevated insulin levels showed a nonsignificant positive association with E-DII scores comparing quartile 4 to quartile 1 (Table 4-6). Among men, a significant negative association was observed between low insulin levels and E-DII scores comparing quartile 4 to quartile 1 ($OR_{Quartile\ 4vs1,} = 0.47$, 95 CI: [0.25, 0.87]). Among women, nonsignificant negative associations were observed for low and high insulin levels and E-DII scores comparing quartile 4 to quartile 1 (Table 4-7).

Waist Circumference. The multivariable logistic regression assessing the odds of abdominal obesity showed a nonsignificant positive association with E-DII scores comparing quartile 4 to quartile 1 (Table 4-6). Among men, those in E-DII quartile 4 experienced a nonsignificant increased odds in abdominal obesity compared to individuals in quartile 1. Among women, those in E-DII quartile 4 experience a nonsignificant decreased odds of abdominal obesity compared to individuals in quartile 1 (Table 4-7).

High-Density Lipoprotein (HDL). The multivariable logistic regression assessing the odds of low HDL levels showed a significant positive association with E-DII scores comparing quartile 4 to quartile 1 ($OR_{Quartile\ 4vs1,}$ = 1.23, 95 CI: [1.09, 1.38]) (Table 4-6). Among men, those in E-DII quartile 4 experienced a nonsignificant increased odds of low HDL comparing E-DII quartiles 4 to quartile 1. However, women in quartile 4 experienced a significant increased odds of low HDL levels compared to women in quartile 1 ($OR_{Quartile\ 4vs1,}$ = 1.64, 95 CI: [1.21, 2.24]) (Table 4-7).

Triglycerides. The multivariable logistic regression assessing the odds of elevated triglyceride levels between 150-199 mg/dL showed a nonsignificant positive association with E-DII scores comparing quartile 4 to quartile 1. In contrast, the odds of elevated triglyceride levels ≥200 mg/dL showed a nonsignificant negative association with E-DII scores comparing quartile 4 to quartile 1 (Table 4-6). Among men, those in quartile 4 experienced a significantly increased odds of triglyceride levels between 150-199 mg/dL compared to those in quartile 1 ($OR_{Quartile\ 4vs1,}$ = 2.00, 95 CI: [1.22, 3.29]). Among women, those in quartile 4 experience a nonsignificant associations with elevated triglyceride levels compared to those in quartile 1 (Table 4-7).

Metabolic Syndrome (MetS). The multivariable logistic regression assessing the odds of MetS showed a nonsignificant positive association with E-DII scores comparing individuals in quartile 4 to individuals in quartile 1 (Table 4-6). Among men, those in quartile 4 experienced a nonsignificant positive association with MetS compared to those in quartile 1. Among women, those in quartile 4 experienced a nonsignificant positive association with MetS compared to those in quartile 1 (Table 4-7).

4.4 Discussion

Among SJLIFE participants, those with pro-inflammatory diets were found to have a lower odds of elevated hs-CRP >3 mg/dL. Furthermore, participants with pro-inflammatory diets were found to have a greater odds of insulin resistance (HOMA-IR), and low HDL cholesterol. In addition, those with pro-inflammatory diets had a lower odds of diabetes (hemoglobin A1C ≥6.5%). Among men, those with pro-inflammatory diets were found to have greater odds of insulin resistance (HOMA-IR) and elevated triglycerides (150-199 mg/dL). Men with proinflammatory diets also had a lower odds of low insulin levels. Among women, those with pro-inflammatory diets had a greater odds of insulin resistance (HOMA-IR) and low HDL cholesterol. Women with pro-inflammatory diets also had a lower odds of diabetes (hemoglobin A1C ≥6.5%), and elevated fasting glucose ≥126 mg/dL. Specifically, HDL cholesterol, insulin resistance, and elevated triglyceride levels are important regulators of cardiovascular disease (CVD) risk among childhood cancer survivors (Baker et al., 2013; Steinberger et al., 2012). CVD has been consistently observed prematurely among this group of survivors and has become one of the main causes of morbidity and mortality in this population (Y. Chen et al., 2020).

Findings from this study were consistent with other research on the DII/E-DII for some outcomes. For example, a previous study by Shivappa et al. found that a pro-inflammatory diet was not associated with CRP levels among adults from the Asklepios study in Belgium (Shivappa, Hébert, et al., 2015). The Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) showed a significant association with E-DII scores. A study by Mazidi et. al., observed associations between diet-associated inflammation and insulin resistance among a representative sample of the US population from the National

Health and Nutrition Examination Surveys (NHANES) (Mazidi et al., 2018). Furthermore, another study observed that elevated CRP levels was associated with an increase in HOMA-IR values (J. Chen et al., 2004). Low levels of HDL was significantly associated with a pro-inflammatory diet overall. Previously, the Supplémentation en Vitamines et Minéraux Anti-oxydants (SU.VI.MAX) study observed a significant positive association between pro-inflammatory diets and low HDL cholesterol levels (Neufcourt et al., 2015). However, after stratification by sex only women were observed to have a significant association with HDL cholesterol indicating that sex as a potential effect modifier of this association. Furthermore, elevated triglyceride levels (150-199 mg/dL) was observed to be associated with a pro-inflammatory diet among men. This observation was significantly different from the association seen in women, indicating that sex may be a potential effect modifier in this association. A previous case-control study had observed a significant association between a proinflammatory and elevated levels of triglycerides among individuals located in Esfahan, Iran (Vahid, Shivappa, Karamati, et al., 2017). Although no significant associations were observed between pro-inflammatory diets and some metabolic outcomes (Glucose, triglycerides, WC, and MetS), few studies have supported this finding. A study by Sokol et al. found that a pro-inflammatory diet was not associated with elevated levels of fasting glucose, elevated levels of triglycerides, or an elevated risk of MetS among individuals from the Polish-Norwegian (PONS) study (Sokol et al., 2016). Furthermore, a study by Neufcourt et al. found that among the SU.VI.MAX study, no significant association was a proinflammatory diet and specific components of the MetS, such as glucose and WC (Neufcourt et al., 2015). A study among Iranian adults found no association between the DII and MetS (Ghorabi et al., 2019). Finally, a study by Wirth et

al., found that among police officers, a pro-inflammatory diet was not associated with MetS; however, high DII scores were observed to be associated with a component of MetS, glucose intolerance (M. Wirth et al., 2014).

Our study also reported several inconsistencies compared to previous research. A pro-inflammatory diet was associated with a decreased odds of hemoglobin A1C ≥ 6.5 %. In addition, this study found no association between the E-DII and hemoglobin A1C (≥ 5.7% and 5.7-6.4%), fasting glucose, insulin, waist circumference, triglycerides, and MetS comparing quartile 4 (most pro-inflammatory) to quartile 1 (most anti-inflammatory). Previous research has predominantly reported significant positive associations between a pro-inflammatory diet and hemoglobin A1C (Denova-Gutiérrez et al., 2018; Vahid, Shivappa, Karamati, et al., 2017). A significant increase in levels of fasting glucose has been observed among individuals who consume pro-inflammatory diets (Vahid, Shivappa, Karamati, et al., 2017). A study by Vahid et al., found that a pro-inflammatory diet was associated with a significant increase in triglyceride levels among individuals from an Iranian case-control study (Vahid, Shivappa, Karamati, et al., 2017). Furthermore, a previous study also found no significant association between a pro-inflammatory diet and waist circumference among French Adults (Neufcourt et al., 2015). The vast majority of literature investigating the association between diet-associated inflammation and MetS has found that a pro-inflammatory diet increases the risk of developing MetS (Canto-Osorio, Denova-Gutierrez, Sánchez-Romero, Salmerón, & Barrientos-Gutierrez, 2020; Mazidi et al., 2018; Neufcourt et al., 2015; Nikniaz, Nikniaz, Shivappa, & Hébert, 2018; C. M. Phillips et al., 2018a).

Among SJLIFE participants, hs-CRP was not associated with a pro-inflammatory diet. Although no association is observed with hs-CRP, other inflammatory markers may have provided more insight into the relationship between dietary intake and inflammation. For example, a study by Shivappa et al., found an association between the consumption of a pro-inflammatory diet and elevated levels of IL-6 (Shivappa, Hébert, et al., 2015). A possible explanation for the lack of an association between a pro-inflammatory diet, MetS, and some of its components is lack of adjustment for other potential confounders. Furthermore, inconsistent consumption of pro-inflammatory diet may have been insufficient to establish the exposure in the SJLIFE study population. In addition, survivors and controls that consume pro-inflammatory diets may already be suffering from comorbid conditions that require interventions or treatment regimens (M. Wirth et al., 2014). Childhood cancer survivors are at a dramatically increased risk of chronic conditions compared to the general population (Howell et al., 2020).

Strengths of this study include the ability to perform direct medical assessments on a large cohort of childhood cancer survivors, and the robust characterization of the cancer-, health behavior-, and treatment-related exposures that provide researchers with the unique opportunity to understand the effects of cancer and cancer-related treatments on the health of childhood cancer survivors throughout their lives (Howell et al., 2020). Despite its strengths, this study is limited by methodological tools used in collecting dietary information, specifically the use of FFQ methodology to assess dietary intake. Rarely, other studies may use other dietary assessment methods in addition to FFQ methodology, such as 24-hour recalls and food diaries (Shivappa, Hebert, Marcos, et al., 2017). Second, hs-CRP is a measure of inflammation that is non-specific to the source of inflammation

making causal inference difficult. Furthermore, the small sample of SJLIFE participants with available hs-CRP values limit the strength of the results of the validation analysis by the potential introduction of selection bias. Additionally, the E-DII is a literature-based assessment of diet-associated inflammatory potential. Inference may be limited by the studies examining dietary intake of non-cancer survivors, specifically non-childhood cancer survivors (Sen et al., 2015).

In conclusion, a pro-inflammatory diet has been observed to have important relevance to a variety of adverse metabolic health outcomes. However, the relevance of diet-associated inflammation on metabolic outcomes among childhood cancer survivors had not yet been studied. This novel study is the first to link diet-associated inflammation to metabolic health among childhood cancer survivors. However, the results of this study show no association between diet-associated inflammation and hs-CRP levels. This may be limited by the number of participants with available hs-CRP information. Cohort studies with a larger number of childhood cancer survivors with available hs-CRP data are needed to gain further understanding of whether a pro-inflammatory diet predicts hs-CRP levels among this vulnerable population. Furthermore, the results of this study suggest an association between the E-DII and some metabolic health outcomes; however, the cross-sectional nature of this study, the use of FFQ methodology, and a limited number of food parameters available may limit these conclusions (Sokol et al., 2016). Overall, the E-DII may be an effective tool for intervention strategies that promote an anti-inflammatory diet among childhood cancer survivors toward improving metabolic health (insulin resistance, HDL cholesterol) and reducing CVD morbidity and mortality among childhood cancer survivors. Long-term follow up of survivors should include counseling that promotes

awareness of the negative impact that unhealthy behaviors can have on their metabolic health (Danielle Novetsky Friedman et al., 2019). Future studies may seek to understand the mechanisms linking diet-associated inflammation with metabolic health in this vulnerable group.

Table 4-1. Distribution of characteristics across E-DII quartiles SJLIFE, United States 2007-2012

E-DII Quartile	Quartile 1 (-5.844, -1.497)	Quartile 2 (-1.497, 0.472)	Quartile 3 (0.472, 1.887)	Quartile 4 (1.887, 4.569)	
Characteristics	(N = 1130)	(N = 1130)	(N = 1130)	(N = 1130)	p-value [a,b]
Study Population					<.0001
Survivor	927 (82%)	975 (86%)	1011 (89%)	1019 (90%)	
Control	203 (18%)	155 (14%)	119 (11%)	111 (10%)	
Age (years)	30.6 (12.2)	29.5 (12.4)	28.9 (13.6)	27.6 (12.6)	<.0001
Sex					<.0001
Male	403 (36%)	569 (50%)	637 (56%)	722 (64%)	
Female	727 (64%)	561 (50%)	493 (44%)	408 (36%)	
Race/Ethnicity					<.0001
White	988 (87%)	942 (83%)	928 (82%)	905 (80%)	
Black	98 (9%)	154 (14%)	183 (16%)	206 (18%)	
Other	44 (4%)	34 (3%)	19 (2%)	19 (2%)	
Education					<.0001
0-12 Grade, did not graduate	34 (3%)	73 (7%)	108 (11%)	145 (14%)	
HS Diploma or GED	110 (11%)	182 (18%)	209 (21%)	293 (29%)	
Some College or Training	294 (29%)	363 (35%)	388 (39%)	392 (39%)	
College Graduate	571 (57%)	408 (40%)	298 (30%)	178 (18%)	
BMI (kg/m)					<.0001
<25	509 (45%)	439 (39%)	419 (37%)	493 (44%)	
25-29	324 (29%)	317 (28%)	357 (32%)	275 (24%)	
≥30	297 (26%)	374 (33%)	354 (31%)	362 (32%)	
Smoking					<.0001
Ever Smokers	243 (22%)	293 (26%)	345 (31%)	432 (39%)	
Never Smokers	865 (78%)	814 (74%)	754 (69%)	666 (61%)	
Heavy Drinking					<.0001
Yes	51 (5%)	66 (6%)	107 (10%)	103 (10%)	
No	1047 (95%)	1031 (94%)	966 (90%)	974 (88%)	
Binge Drinking					0.01
Yes	557 (50%)	489 (44%)	557 (50%)	566 (51%)	
No	547 (50%)	614 (56%)	536 (49%)	526 (48%)	
Physical Activity					<.0001
Meets CDC	739 (65%)	590 (52%)	539 (48%)	490 (43%)	

Does not meet CDC	391 (35%)	540 (48%)	591 (52%)	640 (57%)	
Type of Cancer					<.0001
ALL	274 (24%)	319 (28%)	309 (27%)	278 (25%)	
CNS Tumors	91 (8%)	136 (12%)	163 (14%)	139 (12%)	
Hodgkin Lymphoma	142 (13%)	106 (9%)	106 (9%)	111 (10%)	
Sarcomas	104 (9%)	133 (12%)	125 (11%)	148 (13%)	
Embryonal Tumors	115 (10%)	103 (9%)	115 (10%)	157 (14%)	
Other	199 (18%)	176 (16%)	191 (17%)	184 (16%)	
No cancer	205 (18%)	157 (14%)	121 (11%)	113 (10%)	
Radiation					0.32
Yes	534 (47%)	551 (49%)	578 (51%)	555 (49%)	
No	596 (52%)	579 (51%)	552 (49%)	575 (51%)	
Cranial Radiation					0.02
Yes	209 (19%)	257 (23%)	263 (23%)	215 (19%)	
No	921 (81%)	873 (77%)	867 (77%)	915 (81%)	
Chest Radiation					0.37
Yes	14 (1%)	10 (1%)	20 (2%)	16 (1%)	
No	1116 (99%)	1120 (99%)	1110 (98%)	1114 (99%)	
Whole Abdomen Radiation					0.44
Yes	23 (2%)	20 (2%)	29 (3%)	30 (3%)	
No	1107 (98%)	1110 (98%)	1101 (97%)	1100 (97%)	
Right Abdomen Radiation					0.14
Yes	2 (1%)	10 (1%)	6 (1%)	10 (1%)	
No	1128 (99%)	1120 (99%)	1124 (99%)	1120 (99%)	
Left Abdomen Radiation					0.06
Yes	4 (1%)	4 (1%)	5 (1%)	13 (1%)	
No	1126 (99%)	1126 (99%)	1125 (99%)	1117 (99%)	
Chemotherapy					0.09
Yes	458 (41%)	515 (46%)	480 (42%)	472 (42%)	
No	672 (59%)	615 (54%)	650 (58%)	658 (58%)	
Alkylating Agent					0.003
Yes	575 (51%)	637 (56%)	608 (54%)	657 (58%)	
No	555 (49%)	493 (44%)	522 (46%)	473 (42%)	
Anthracyclines					0.004
Yes	545 (48%)	556 (49%)	544 (48%)	618 (55%)	
No	585 (52%)	574 (51%)	586 (52%)	512 (45%)	
Antimetabolites					0.09
Yes	458 (41%)	515 (46%)	480 (42%)	472 (42%)	
No	672 (59%)	615 (54%)	650 (58%)	658 (58%)	

Corticosteroids					0.37
Yes	9 (1%)	8 (1%)	8 (1%)	3 (1%)	
No	1121 (99%)	1122 (99%)	1122 (99%)	1127 (99%)	
Glucocorticoids					0.18
Yes	438 (39%)	460 (41%)	452 (40%)	412 (36%)	
No	692 (61%)	670 (59%)	678 (60%)	718 (64%)	
Surgery					0.08
Yes	347 (72%)	410 (77%)	450 (78%)	434 (76%)	
No	128 (25.05)	118 (23.09)	126 (24.66)	139 (27.20)	
Statin					0.80
Yes	29 (3%)	36 (3%)	36 (3%)	34 (3%)	
No	1101 (97%)	1094 (97%)	1094 (97%)	1096 (97%)	
CRP (mg/L)	5.1 ± 10.0	3.7 ± 5.3	5.1 ± 10.8	3.4 ± 6.1	0.31
CRP (Binary)					0.46
≤ 3 mg/L	61 (62%)	71 (63%)	59 (59%)	73 (70%)	
> 3 mg/L	37 (38%)	42 (37%)	41 (41%)	32 (30%)	
CRP (Categorical)					0.02
<1 mg/L	37 (38%)	29 (26%)	39 (39%)	48 (46%)	
1-3 mg/L	24 (24%)	42 (37%)	20 (20%)	25 (24%)	
>3 mg/L	37 (38%)	42 (37%)	41 (41%)	32 (30%)	

Data presented are Median (IQR), N (%).

[a] Continuous Variables were compared using ANOVA

[b] Categorical Variables were compared using Chi-square test

Table 4-2. Dietary Intake by Energy-Adjusted DII Quartiles St. Jude Lifetime Study, United States 2007-2012

E-DII Quartile	Quartile 1 (-5.844, -1.499)	Quartile 2 (-1.499, 0.458)	Quartile 3 (0.458, 1.885)	Quartile 4 (1.885, 4.569)	
Variable	(N = 1108)	(N = 1108)	(N = 1108)	(N = 1108)	p-trend
Energy (kcal)	1,673.12 ± 818.14	2,017.65 ± 1,331.00	2,320.33 ± 1,725.80	2,524.05 ± 1,529.19	<.0001
Carbohydrate (g/1,000 kcal)	200.96 ± 105.19	234.70 ± 153.68	269.28 ± 190.62	301.69 ± 176.39	<.0001
Protein (g/1,000 kcal)	71.98 ± 38.68	82.02 ± 63.63	89.91 ± 77.24	89.33 ± 62.33	<.0001
Fat (g/1,000 kcal)	66.03 ± 33.81	83.37 ± 57.02	97.08 ± 77.13	105.42 ± 69.38	<.0001
Saturated Fat (g/1,000 kcal)	19.32 ± 10.24	26.34 ± 17.76	31.63 ± 24.50	35.57 ± 22.90	<.0001
MUFA (g/1,000 kcal)	25.85 ± 13.38	32.47 ± 22.47	37.81 ± 30.63	41.11 ± 27.44	<.0001
PUFA (g/1,000 kcal)	15.79 ± 8.55	17.93 ± 12.58	19.81 ± 16.16	20.21 ± 14.08	<.0001
Trans Fats (g/1,000 kcal)	1.92 ± 1.21	2.95 ± 2.21	3.65 ± 2.95	4.37 ± 3.05	<.0001
Omega-3 Fatty Acids (g/1,000 kcal)	1.70 ± 1.00	1.87 ± 1.38	2.00 ± 1.66	1.91 ± 1.42	<.0001
Cholesterol (mg/1,000 kcal)	226.46 ± 160.96	291.97 ± 239.99	338.81 ± 295.82	358.67 ± 256.93	<.0001
Fe (mg/1,000 kcal)	14.19 ± 7.17	14.57 ± 10.30	15.33 ± 12.14	14.67 ± 9.60	0.05
Zn (mg/1,000 kcal)	11.10 ± 7.22	12.64 ± 10.95	13.38 ± 11.21	13.21 ± 9.24	<.0001
Mg (mg/1,000 kcal)	336.32 ± 167.21	310.68 ± 202.32	304.05 ± 223.36	271.34 ± 165.64	<.0001
Se (mcg/1,000 kcal)	92.11 ± 50.87	107.03 ± 81.72	118.34 ± 102.55	117.35 ± 82.75	<.0001
Vitamin A (RAE/1,000 kcal)	1,015.41 ± 546.50	867.42 ± 726.45	760.10 ± 596.40	630.98 ± 412.14	<.0001
Thiamin (mg/1,000 kcal)	1.57 ± 0.86	1.63 ± 1.21	1.73 ± 1.44	1.61 ± 1.07	0.01
Riboflavin (mg/1,000 kcal)	2.10 ± 1.08	2.18 ± 1.41	2.26 ± 1.62	2.09 ± 1.27	0.01
Vitamin B6 (mg/1,000 kcal)	2.16 ± 1.18	2.06 ± 1.54	2.05 ± 1.66	1.79 ± 1.16	<.0001
Vitamin B12 (mcg/1,000 kcal)	5.25 ± 3.76	5.91 ± 6.02	6.16 ± 5.66	5.77 ± 4.24	0.0002

Vitamin C (mg/1,000 kcal)	129.89 ± 83.17	111.00 ± 90.53	101.00 ± 90.93	82.65 ± 75.80	<.0001
Vitamin D (IU/1,000 kcal)	168.53 ± 149.17	170.00 ± 146.45	162.77 ± 142.75	139.19 ± 113.99	<.0001
Vitamin E (mg/1,000 kcal)	9.10 ± 4.86	8.11 ± 5.27	7.95 ± 6.01	7.42 ± 4.95	<.0001
Niacin (mg/1,000 kcal)	21.88 ± 12.72	23.39 ± 18.95	24.94 ± 21.78	23.26 ± 15.93	0.0007
Dietary Fiber (g/1,000 kcal)	20.51 ± 10.04	17.36 ± 11.10	16.27 ± 11.73	14.20 ± 9.02	<.0001
Beta-carotene (mcg/1,000 kcal)	6,725.36 ± 4,564.99	4,372.38 ± 4,072.93	3,038.47 ± 2,819.24	1,810.04 ± 1,556.39	<.0001
Folic Acid (mcg/1,000 kcal)	149.23 ± 126.06	160.33 ± 136.09	180.35 ± 171.01	170.43 ± 124.39	<.0001
Isoflavones (mg/1,000 kcal)	3.62 ± 8.62	1.64 ± 3.01	1.69 ± 2.90	1.54 ± 1.52	<.0001

[a] Values are Means ± SD. E-DII, Energy-adjusted Dietary Inflammatory Index; MUFA, Monounsaturated Fatty Acids; PUFA, Polyunsaturated Fatty Acids; Fe, Iron; Zn, Zinc; Mg, Magnesium; Se, Selenium

Table 4-3. Beta estimates and confidence intervals for association between E-DII and CRP, SJLIFE, 2007-2012

	Model 1[a]		Model 2[b]		Model 3[c]	
	B (95% CI)	P-value	B (95% CI)	P-value	B (95% CI)	P-value
CRP (continuous)	-0.09 (-0.20, 0.03)	0.14	-0.06 (-0.18, 0.06)	0.31	-0.08 (-0.20,0.03)	0.14
CRP (binary)						
≤ 3mg/L	ref		ref		ref	
> 3mg/L	-0.06 (-0.16, 0.04)	0.25	-0.04 (-0.15, 0.06)	0.42	-0.07 (-0.20, 0.07)	0.32
CRP (categorical)						
< 1 mg/L	ref		ref		ref	
1-3 mg/L	- 0.09 (-0.21, 0.03)	0.15	-0.03 (-0.15, 0.09)	0.65	-0.05 (-0.19, 0.09)	0.48
>3 mg/L	-0.10 (-0.21, 0.02)	0.1	-0.06 (-0.18, 0.06)	0.36	-0.09 (-0.25, 0.06)	0.24

Data presented are β (95% CI).

[a] Unadjusted Model (CRP = DII).

[b] Age-adjusted Model

[c] Multivariable Model: adjusted for age, gender, race, education, BMI, smoking , heavy drinking, physical activity, radiation therapy, chemotherapy, and survivor status. CRP, C-reactive protein; E-DII, Energy-adjusted Dietary Inflammatory Index;

Table 4-4. Beta estimates and confidence intervals for association between E-DII Quartiles and CRP, SJLIFE, 2007-2012

		E-DII Quartile							
		Quartile 1 (-5.844, -1.499)		Quartile 2 (-1.499, 0.458)		Quartile 3 (0.458, 1.885)		Quartile 4 (1.885, 4.569)	
		β (95 % CI)	p-value	β (95% CI)	p-value	β (95% CI)	p-value	β (95% CI)	p-value
Continuous	CRP								
	Model 1[a]	0.0 (ref)	ref	0.32 (-0.36, 0.99)	0.35	0.02 (-0.68, 0.73)	0.95	-0.55 (-1.24, 0.15)	0.12
	Model 2[b]	0.0 (ref)	ref	0.35 (-0.32, 1.02)	0.31	0.12 (-0.59, 0.83)	0.74	-0.42 (-1.12, 0.28)	0.24
	Model 3[c]	0.0 (ref)	ref	0.06 (-0.56, 0.67)	0.85	0.004 (-0.65, 0.66)	0.99	-0.59 (-1.26, 0.08)	0.09
Binary	CRP (reference ≤ 3mg/L)								
	Model 1[a]	0.0 (ref)	ref	-0.14 (-0.50, 0.23)	0.46	-0.16 (-0.56, 0.23)	0.42	0.37 (-0.04, 0.78)	0.07
	Model 2[b]	0.0 (ref)	ref	-0.12 (-0.48, 0.25)	0.54	-0.18 (-0.58, 0.21)	0.36	0.33 (-0.08, 0.74)	0.11
	Model 3[c]	0.0 (ref)	ref	-0.0007 (-0.43, 0.43)	0.99	0.32 (-0.13, 0.77)	0.17	-0.42 (-0.91, 0.06)	0.09
Categorical	CRP (reference < 1mg/L)								
	Model 1[a] (1-3 mg/L)	0.0 (ref)	ref	**0.72 (0.30, 1.13)**	**0.001**	-0.32 (-0.78, 0.13)	0.17	-0.31 (-0.73, 0.12)	0.16
	Model 1[a] (> 3 mg/L)	0.0 (ref)	ref	**0.48 (0.06, 0.91)**	**0.03**	0.04 (-0.38, 0.45)	0.86	**-0.51 (-0.94, -0.08)**	**0.02**
	Model 2[b] (1-3 mg/L)	0.0 (ref)	ref	**0.68 (0.25, 1.11)**	**0.002**	-0.26 (-0.72, 0.21)	0.28	-0.18 (-0.62, 0.26)	0.42
	Model 2[b] (> 3 mg/L)	0.0 (ref)	ref	**0.46 (0.03, 0.89)**	**0.04**	0.08 (-0.34, 0.50)	0.7	-0.42 (-0.86, 0.02)	0.06

Model 3[c] (1-3 mg/L)	0.0 (ref)	ref	**0.60 (0.16, 1.03)**	**0.01**	-0.05 (-0.48, 0.39)	0.83	-0.42 (-0.88, 0.03)	0.07
Model 3[c] (> 3 mg/L)	0.0 (ref)	ref	0.52 (-0.08, 1.12)	0.09	0.37 (-0.21, 0.95)	0.21	**-0.77 (-1.39, -0.14)**	**0.02**

Data presented are β (95% CI).

[a] Unadjusted Model (CRP = DII).

[b] Age-adjusted Model

[c] Multivariable Model: adjusted for age, gender, race, education, BMI, smoking , heavy drinking, physical activity, radiation therapy, chemotherapy, and survivor status. CRP, C-reactive protein; E-DII, Energy-adjusted Dietary Inflammatory Index;

Table 4-5. Odds Ratios and confidence intervals for association between E-DII Quartiles and CRP, SJLIFE, 2007-2012

		E-DII Quartile			
		Quartile 1 (-5.844, -1.499)	Quartile 2 (-1.499, 0.458)	Quartile 3 (0.458, 1.885)	Quartile 4 (1.885, 4.569)
		OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Binary	CRP (reference ≤ 3mg/L)				
	Model 1[a]	1 (ref)	1.11 (0.61, 2.01)	1.15 (0.61, 2.14)	0.66 (0.34, 1.26)
	Model 2[b]	1 (ref)	1.13 (0.62, 2.06)	1.22 (0.65, 2.30)	0.71 (0.37, 1.39)
	Model 3[c]	1 (ref)	0.99 (0.65, 1.53)	1.37 (0.88, 2.16)	0.65 (0.40, 1.07)
Categorical	CRP (reference < 1mg/L)				
	Model 1[a] (1-3 mg/L)	1 (ref)	**2.23 (1.11, 4.49)**	0.79 (0.38, 1.67)	0.80 (0.40, 1.63)
	Model 1[a] (> 3 mg/L)	1 (ref)	1.64 (0.82, 3.28)	1.05 (0.53, 2.08)	0.61 (0.30, 1.23)
	Model 2[b] (1-3 mg/L)	1 (ref)	**2.53 (1.23, 5.22)**	0.99 (0.46, 2.14)	1.07 (0.51, 2.24)
	Model 2[b] (> 3 mg/L)	1 (ref)	1.80 (0.89, 3.65)	1.23 (0.61, 2.48)	0.75 (0.36, 1.54)
	Model 3[c] (1-3 mg/L)	1 (ref)	**1.82 (1.18, 2.81)**	0.95 (0.62, 1.48)	0.65 (0.42, 1.03)
	Model 3[c] (> 3 mg/L)	1 (ref)	1.68 (0.93, 3.06)	1.45 (0.81, 2.60)	**0.47 (0.25, 0.87**)

Data presented are Odds Ratios (95% CI).

[a] Unadjusted Model (CRP = DII).

[b] Age-adjusted Model

[c] Multivariable Model: adjusted for age, gender, race, education, BMI, smoking , heavy drinking, physical activity, radiation therapy, chemotherapy, and survivor status. CRP, C-reactive protein; E-DII, Energy-adjusted Dietary Inflammatory Index;

Table 4-6. Odds Ratios and confidence intervals for association between E-DII Quartiles and Metabolic Outcomes, SJLIFE, 2007-2012

		E-DII Quartile			
		Quartile 1 (-5.844, -1.497)	Quartile 2 (-1.497, 0.472)	Quartile 3 (0.472, 1.887)	Quartile 4 (1.887, 4.569)
		OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Binary [a]	Hemoglobin A1C (reference < 5.7%)				
	≥ 5.7%	1 (ref)	1.11 (0.96, 1.28)	**1.22 (1.06, 1.40)**	0.97 (0.92, 1.12)
	HOMA-IR (reference < 2.86)				
	≥ 2.86	1 (ref)	1.06 (0.94, 1.19)	1.04 (0.92, 1.17)	**1.28 (1.13, 1.44)**
	Glucose (reference < 100 mg/dL)				
	≥ 100 mg/dL	1 (ref)	1.11 (0.98, 1.25)	1.02 (0.91, 1.16)	0.98 (0.86, 1.12)
	Waist Circumference				
	Abdominal obesity	1 (ref)	0.94 (0.79, 1.12)	1.08 (0.91, 1.28)	1.05 (0.87, 1.26)
	HDL				
	Low	1 (ref)	0.97 (0.86, 1.08)	1.03 (0.92, 1.16)	**1.23 (1.09, 1.38)**
	Metabolic Syndrome				
	Yes	1 (ref)	0.95 (0.76, 1.19)	**1.29 (1.05, 1.60)**	1.08 (0.86, 1.36)
Categorical [a]					
	Hemoglobin A1C (reference < 5.7%)				
	5.7 - 6.4 %	1 (ref)	1.11 (0.96, 1.28)	**1.22 (1.06, 1.40)**	0.97 (0.83, 1.13)

≥ 6.5 %	1 (ref)	1.22 (0.92, 1.62)	**1.32 (1.01, 1.73)**	**0.67 (0.48, 0.94)**
Insulin				
Low	1 (ref)	**0.63 (0.47, 0.85)**	1.21 (0.94, 1.54)	0.90 (0.69, 1.18)
High	1 (ref)	1.01 (0.85, 1.19)	0.91 (0.76, 1.08)	1.04 (0.88, 1.24)
Triglycerides (reference = < 150 mg/dL)				
150 – 199 mg/dL	1 (ref)	0.93 (0.82, 1.06)	**1.16 (1.02, 1.31)**	1.03 (0.90, 1.18)
≥ 200 mg/dL	1 (ref)	0.98 (0.83, 1.16)	1.14 (0.97, 1.34)	0.93 (0.78, 1.12)
Glucose (reference < 100 mg/dL)				
100 – 125 mg/dL	1 (ref)	1.22 (0.97, 1.53)	1.06 (0.83, 1.34)	1.13 (0.88, 1.44)
≥ 126 mg/dL	1 (ref)	1.28 (0.98, 1.68)	1.19 (0.91, 1.56)	0.76 (0.55, 1.04)

Data presented are Odds Radios (95% CI).

[a] Multivariable Model: adjusted for age, gender, race, education, BMI, smoking, heavy drinking, PA, radiation therapy and survivor status. HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; HDL, High Density Lipoprotein;

Table 4-7. Odds Ratios and confidence intervals for association between E-DII Quartiles and Metabolic Outcomes by Sex, SJLIFE, 2007-2012

Male			Q1	Q2	Q3	Q4
	Binary	Hemoglobin A1C				
		≥ 5.7%	1.00 (ref)	1.46 (0.98, 2.19)	**1.73 (1.16, 2.58)**	1.48 (0.99, 2.22)
		HOMA-IR				
		≥ 2.86	1.00 (ref)	**1.54 (1.12, 2.13)**	**1.45 (1.04, 2.01)**	**2.06 (1.48, 2.86)**
		Glucose				
		≥ 100 mg/dL	1.00 (ref)	1.17 (0.86, 1.58)	1.02 (0.75, 1.40)	1.18 (0.87, 1.62)
		Waist Circumference				
		Abdominal obesity	1.00 (ref)	1.15 (0.71, 1.86)	1.21 (0.75, 1.97)	1.41 (0.86, 2.30)
		HDL				
		Low	1.00 (ref)	1.23 (0.88, 1.73)	1.20 (0.85, 1.68)	1.36 (0.97, 1.91)
		Metabolic Syndrome				
		Yes	1.00 (ref)	1.38 (0.75, 2.55)	**1.95 (1.07, 3.54)**	1.81 (0.99, 3.31)
	Categorical					
		Hemoglobin A1C				
		5.7 - 6.4 %	1.00 (ref)	1.29 (0.84, 1.99)	**1.63 (1.07, 2.49)**	1.44 (0.94, 2.20)
		≥ 6.5 %	1.00 (ref)	**2.51 (1.03, 6.14)**	2.33 (0.94, 5.75)	1.61 (0.63, 4.09)
		Insulin				
		Low	1.00 (ref)	**0.37 (0.19, 0.74)**	0.74 (0.41, 1.32)	**0.47 (0.25, 0.87)**
		High	1.00 (ref)	1.15 (0.71, 1.85)	0.81 (0.49, 1.33)	1.25 (0.77, 2.01)
		Triglycerides				
		150 – 199 mg/dL	1.00 (ref)	**1.72 (1.05, 2.84)**	**1.99 (1.21, 3.26)**	**2.00 (1.22, 3.29)**
		≥ 200 mg/dL	1.00 (ref)	1.12 (0.75, 1.68)	1.00 (0.66, 1.50)	1.00 (0.66, 1.52)
		Glucose				
		100 – 125 mg/dL	1.00 (ref)	1.10 (0.81, 1.51)	0.96 (0.70, 1.32)	1.15 (0.83, 1.60)
		≥ 126 mg/dL	1.00 (ref)	1.99 (0.88, 4.53)	1.83 (0.81, 4.16)	1.67 (0.73, 3.84)
Female			Q1	Q2	Q3	Q4
	Binary [a]	Hemoglobin A1C				

	≥ 5.7%	1.00 (ref)	**1.67 (1.18, 2.36)**	1.41 (0.98, 2.04)	0.98 1.50)	(0.64,
	HOMA-IR					
	≥ 2.86	1.00 (ref)	**1.40 (1.05, 1.87)**	**1.46 (1.09, 1.98)**	**1.51 2.10)**	**(1.08,**
	Glucose					
	≥ 100 mg/dL	1.00 (ref)	1.30 (0.94, 1.78)	1.15 (0.82, 1.62)	0.87 1.27)	(0.59,
	Waist Circumference					
	Abdominal obesity	1.00 (ref)	0.89 (0.60, 1.33)	0.99 (0.66, 1.49)	0.84 1.34)	(0.52,
	HDL					
	Low	1.00 (ref)	1.17 (0.90, 1.54)	1.31 (0.99, 1.75)	**1.64 2.24)**	**(1.21,**
	Metabolic Syndrome					
	Yes	1.00 (ref)	1.44 (0.81, 2.59)	1.40 (0.76, 2.57)	1.07 2.16)	(0.53,
Categorical [a]	Hemoglobin A1C					
	5.7 - 6.4 %	1.00 (ref)	**1.93 (1.33, 2.82)**	**1.58 (1.06, 2.37)**	1.25 1.98)	(0.79,
	≥ 6.5 %	1.00 (ref)	0.95 (0.49, 1.84)	0.94 (0.47, 1.86)	**0.30 0.84)**	**(0.11,**
	Insulin					
	Low	1.00 (ref)	0.54 (0.30, 1.00)	0.76 (0.41, 1.41)	0.80 1.60)	(0.40,
	High	1.00 (ref)	0.72 (0.47, 1.11)	0.86 (0.55, 1.35)	0.61 1.01)	(0.37,
	Triglycerides					
	150 – 199 mg/dL	1.00 (ref)	0.81 (0.52, 1.25)	0.21 (0.78, 1.88)	1.00 1.64)	(0.61,
	≥ 200 mg/dL	1.00 (ref)	1.05 (0.65, 1.68)	1.70 (1.07, 2.70)	1.07 1.86)	(0.61,
	Glucose					
	100 – 125 mg/dL	1.00 (ref)	1.31 (0.93, 1.84)	1.20 (0.84, 1.72)	1.02 1.52)	(0.68,
	≥ 126 mg/dL	1.00 (ref)	1.20 (0.62, 2.32)	0.94 (0.46, 1.92)	**0.29 0.84)**	**(0.10,**

Data presented are Odds Radios (95% CI).

[a] Multivariable Model: adjusted for age, gender, race, education, BMI, smoking, heavy drinking, PA, radiation therapy, and survivor status. HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; HDL, High Density Lipoprotein;

CHAPTER 5

ASSOCIATIONS BETWEEN THE ENERGY-ADJUSTED DIETARY INFLAMMATORY INDEX (E-DII) AND ANXIETY AND DEPRESSIVE SYMPTOMS AMONG CHILDHOOD CANCER SURVIVORS: THE ST. JUDE LIFETIME COHORT STUDY (SJLIFE)

Abstract

Introduction: Currently, the 5-year survival rate of childhood cancers exceeds 84% in the United States. These survivors remain at higher risk for adverse health outcomes later in life. In addition to the increased burden of chronic diseases, including second primary cancers and cardiovascular disease, they often have mental health needs that remain unmet. These unmet needs can result in a significant increase in symptoms of anxiety and depression. Diet-associated inflammation has been established as an important predictor of adverse psychological outcomes, including depression and anxiety. However, this association has not been established in a childhood cancer population.

Methods: Participants were childhood cancer survivors from the St. Jude Lifetime Cohort Study (SJLIFE). Diet-associated inflammation was quantified using the Dietary Inflammatory Index (DII®) and energy-adjusted DII (E-DII^{TM}) scores, which were calculated from the 2005 Block Food Frequency Questionnaire (FFQ). The Brief Symptom

Inventory-18 (BSI-18) was used to query acute symptoms of anxiety and depression. Linear and logistic regression models were used to evaluate associations between diet-associated inflammation and symptoms of anxiety and depression. The E-DII was used as a continuous and categorical (quartiles) predictor variable. BSI-18 t-scores were analyzed as both a continuous and a binary (<63 or ≥ 63) response variable.

Results: A sub-sample of 4,317 participants in the SJLIFE cohort with available dietary intake and BSI-18 information was included in this study. The mean age of this sub-sample was 30.8 ± 8.8 years old. There were a total of 447 individuals with a t-score ≥ 63 for anxiety and 582 individuals with a t-score ≥ 63 for depressive symptoms. The mean E-DII score was 0.13 ± 2.16 for SJLIFE participants in this study. After adjusting for confounders, a pro-inflammatory diet was not statistically significantly associated with anxiety (OR = 0.994, 95% CI: [0.94, 1.05]). In contrast, a one-point higher score on the E-DII increased risk for depressive symptoms by 7% (OR =1.07, 95% CI: [1.02, 1.13]). Additionally, an increased odds of depressive symptoms was observed among survivors with the most pro-inflammatory diets (quartile 4) compared to those with the most anti-inflammatory diets (quartile 1) ($OR_{\text{Quartile 4vs1}} = 1.63$, 95% CI: [1.19, 2.23]). Sex-stratified analyses with the E-DII categorized into quartiles revealed statistically significant associations between a pro-inflammatory diet and depressive symptoms for men but not women (Men: $OR_{\text{Quartile 4vs1,}} = 1.94$, 95% CI: [1.18, 3.18]).

Discussion: This is the first study to investigate the association between dietary inflammation and mental health outcomes among childhood cancer survivors. Results are broadly consistent with what has been observed in other adult populations in which associations have been reported between diet-associated inflammation and depression.

This study provides important findings that can inform dietary intervention strategies focused on the reduction of dietary inflammation that can have a significant impact on depressive symptoms in this vulnerable population.

Keywords: anxiety, depression, inflammation, childhood cancer survivors

5.1 Introduction

Currently, childhood cancer is the second leading cause of death among children 5-14 years old in the United States (US) (Ward et al., 2014). However, mortality has dramatically decreased by over 50% since 1975 (Ward et al., 2014). The 5-year survival of childhood cancers now exceeds 84% in the US (Armstrong et al., 2016; Bethesda, 2015; Howell et al., 2020). It is estimated that the number of childhood cancer survivors now exceeds 500,000 (Armstrong et al., 2016; Robison & Hudson, 2014). Survivors of pediatric malignancies remain at high risk for several adverse health events including the recurrence of their initial cancer and other chronic diseases, such as type II diabetes mellitus and cardiovascular diseases (Armstrong et al., 2016; Cardous-Ubbink et al., 2004; Dowling et al., 2010; M. C. Hoffman et al., 2013; S. M. Phillips et al., 2015; Pui et al., 2003; Reulen et al., 2010; Robison & Hudson, 2014). Furthermore, the toxicity of many forms of cancer treatments, such as chemotherapy, can promote the development of treatment-related complications, which may arise several years after the treatment is complete (Friend, Feltbower, Hughes, Dye, & Glaser, 2018). Following diagnosis and treatment for their malignancies, childhood cancer survivors experience an increased risk of several adverse psychological outcomes, including anxiety and depression (Brinkman, Recklitis, Michel, Grootenhuis, & Klosky, 2018).

Survivors of specific childhood malignancies, such as Central Nervous System (CNS) tumors (Friend et al., 2018) and Acute Lymphoblastic Leukemia (ALL) (Kunin-Batson et al., 2016), are reported to have a higher risk of adverse mental health outcomes compared to adults in the general population. Furthermore, evidence indicates that survivors of solid tumors have a higher risk of adverse mental health compared to survivors of hematological cancers (Friend et al., 2018). Other risk factors for poor mental health among childhood cancer survivors include demographic, treatment, and lifestyle factors (Friend et al., 2018). Demographic factors include being a female (Friend et al., 2018; Lehmann et al., 2014; Yi & Syrjala, 2017; Zevon, Neubauer, & Green, 1989), being younger (Yi & Syrjala, 2017), and having lower educational attainment (Yi & Syrjala, 2017). Treatment-related risk factors include radiation (specifically cranial radiation), and chemotherapy (specifically, alkylating agents) (Friend et al., 2018; Kaye, Brinkman, & Baker, 2017). Lifestyle factors include smoking (Yi & Syrjala, 2017), low levels of physical activity (Lown, Phillips, Schwartz, Rosenberg, & Jones, 2015), and a poor diet (Brinkman et al., 2018).

Despite their increased risk for adverse late-effects, childhood cancer survivors are more likely to have insufficient physical activity compared to their siblings and to peers (Lown et al., 2016) and do not meet the dietary recommendations for American adults (F. F. Zhang et al., 2016). Currently, diet as a risk factor for mental health disorders in this population have yet to be thoroughly investigated. Research in other populations indicates that diet plays an important role in mental health among children, adolescents, and adults that were never diagnosed with cancer (Dawson, Dash, & Jack, 2016; O'Neil et al., 2014). Specifically, unhealthy dietary patterns have been observed to increase the risk of adverse

mental health outcomes in these groups (Dawson et al., 2016; Mayr et al., 2018; Ramallal et al., 2017; Tabung et al., 2015). Further, research indicates that diet-associated inflammation is an important predictor of depression (Garcia-Arellano et al., 2019; Polanska et al., 2021; Shakya et al., 2021; Wang et al., 2019). Results for anxiety are more equivocal (Ghazizadeh et al., 2020; C. M. Phillips, Shivappa, Hébert, & Perry, 2018b; Polanska et al., 2021; Shivappa, Hebert, & Rashidkhani, 2017; Shivappa, Hebert, et al., 2018). Diets following informed recommendations are associated with better mental health outcome among adults (Akbaraly et al., 2009; Jacka et al., 2010; Lai et al., 2014; O'Neil et al., 2014).

Instead of focusing on specific nutrients, the emerging field of nutritional psychiatry has prioritized investigating the potential association of mental health with dietary patterns (C. M. Phillips et al., 2018b). For example, a 'Western-style diet' (high in fat) has been observed to be associated with an elevated risk of depressive symptoms (C. M. Phillips et al., 2018b). Potential mechanisms for this association have been observed among mice and suggests that consumption of saturated fatty acids can induce activation of toll-like receptor 4 (TLR4) in hypothalamic microglia. Activation of TLR4 promotes the secretion of pro-inflammatory cytokines, such as TNF-α and IL-1β, indicating a potential mechanism for high fat diets to cause brain inflammation (Melo, Santos, & Ferreira, 2019). Release of TNF-α and IL-1β can negatively affect the hippocampus and may inhibit neurogenesis (Calabrese et al., 2014). Inhibition of neurogenesis has been linked with mental illness (e.g., depression, anxiety, and schizophrenia) among adults (Schoenfeld & Cameron, 2015). Among childhood cancer survivors, >30% consume calories in excess of their recommended caloric intake (J. Cohen et al., 2012; Landy et al., 2013; Teixeira et al.,

2018). Consistent with consuming energy-dense diets, survivors are consistently reported to consume diets that are low in fruit, vegetable, and calcium intake and high in fat intake (Barnea et al., 2015; Stolley et al., 2010; F. F. Zhang et al., 2018; F. F. Zhang & Parsons, 2015). In a study by Teixeira et. al., saturated fatty acids and trans fatty acids promote the onset of chronic inflammation but some polyunsaturated fatty acids, especially omega-3 fatty acids, have been observed to cause a decrease in both inflammation and the risk of chronic disease (Teixeira et al., 2018). Furthermore, a study by Melo et al., expanded on this potential mechanism by reporting that individuals with symptoms of anxiety and depression had lower circulating levels of PUFAs compared to asymptomatic controls (Melo et al., 2019).

Chronic inflammation may be an important factor in the development of adverse health outcomes among childhood cancer survivors. This type of inflammation lacks the negative feedback signaling present in the normal inflammatory response. This feedback signaling results in the discontinuation of the acute inflammatory response (Elenkov et al., 2005; Khan et al., 2018; Mathé et al., 2012). Inadequate dietary intake can lead to a state of chronic inflammation resulting from the inhibition of anti-inflammatory cytokines (Khan et al., 2018; Ramallal et al., 2017; Saita et al., 2014). Dietary intake is related to circulating levels of pro-inflammatory cytokines such as C-reactive Protein (CRP), interleukin 6 (IL-6), and tumor necrosis factor alpha (TNF-α). Pro-inflammatory cytokines can cause inhibition of neurogenesis, which can promote the onset of neuroinflammation (Melo et al., 2019). The most pro-inflammatory diets are associated with an elevated risk of depressive symptoms (C. M. Phillips et al., 2018b). The Dietary Inflammatory Index (DII®) is a tool that was developed to quantify the inflammatory potential of an individual's

diet on a scale that ranges between maximally anti-inflammatory to maximally pro-inflammatory (usually around -5.5 to +5.5). Quantification of the DII, and the refined Energy-adjusted DII (E-DII), were based on a scoring algorithm of peer-reviewed articles published throughout a 60-year span (1950-2010) (Shivappa et al., 2014). Therefore, this study is being conducted in order to assess potential associations between diet-associated inflammation and mental health, including anxiety and depressive symptoms in a cohort of childhood cancer survivors. We predict that high E-DII scores are associated with increased t-scores for anxiety and depression among the SJLIFE cohort. We also predict that a pro-inflammatory diet is associated with symptoms of anxiety and depression in this cohort.

5.2 Methods

Study Population

The St. Jude Lifetime Cohort Study (SJLIFE) began in 2007 at St. Jude Children's Research Hospital (SJCRH) as a retrospective hospital-based study with prospective follow-up of childhood cancer survivors. SJCRH is an NCI-designated Comprehensive Cancer Center that focuses exclusively on the treatment of childhood malignancies and provides comprehensive medical services for children and adolescents with a cancer diagnosis (Hudson et al., 2011). Prior to 2015, the SJLIFE study included adults treated for childhood cancer at SJCRH who had survived at least 10 years (Howell et al., 2020). Following 2015, the cohort expanded to include childhood cancer survivors of all ages who had survived at least 5 years (Howell et al., 2020). In order to be eligible for inclusion in SJLIFE, participants need to satisfy the following criteria: (1) have a history of childhood cancer that was diagnosed and treated at SJCRH between 1962 and 2012 and (2) have

survived a minimum of five years following their diagnosis (Howell et al., 2020). Controls in the SJLIFE study were frequency- matched based on age, sex, and race. SJLIFE survivors were given the opportunity to recommend a friend or non-first degree relative as a potential community control. These individuals completed the same clinical evaluations as survivors and did not have a history of childhood cancer. These participants were referred to as "community controls" because they were recruited from the same general geographic area as survivors. Additional controls were recruited from the Memphis geographic area (Howell et al., 2020). With respect to the current study, eligibility was contingent on the availability of macro-/micronutrient intake information from a food frequency questionnaire and the Brief Symptom Inventory-18 (BSI-18), both described in greater detail below.

Dietary Assessment

Participants in the SJLIFE study completed five questionnaires (i.e., the home survey, the behavior survey, health habits survey, the women's/men's health survey, and the Block Food Frequency questionnaire), totaling 882 items on various health topics. Health topics ranged from: (1) health history and current health status, (2) social and demographic factors, (3) health behaviors, (4) psychosocial functioning, and (5) psychosexual health (Hudson et al., 2011). Specifically, a self-administered Block 2005 Food Frequency Questionnaire (FFQ) was used to collect dietary information. The FFQ assesses the nutritional intake of participants by querying 110 food items eaten in the past 12 months (F. F. Zhang et al., 2018). Completed FFQs were process by Block Dietary Data Systems and used to calculate nutrient intake and both Dietary Inflammatory Index (DII®) and Energy-Adjusted DII (E-DII™) scores.

Dietary Inflammatory Index (DII®) and the Energy-Adjusted DII (E-DII™)

The DII is a tool used to quantify the inflammatory potential of an individuals' dietary intake (Shivappa et al., 2014). The DII assessment is based on each individual's dietary intake reported on the FFQ. Scores are a continuous scale that ranges from maximally anti-inflammatory to maximally pro-inflammatory (theoretically from -9 to +8, but the range usually falls between -5.5 and +5.5). A scoring algorithm from 1,943 peer-reviewed manuscripts was used to calculate DII scores (Shivappa et al., 2014). The manuscripts that were reviewed assessed the effects of individual foods, nutrients, and other bioactive compounds such as flavonoids (termed food parameters) on changes in anti-inflammatory (IL-4 and IL-10) and pro-inflammatory (IL-1β, IL-6, TNF-α, and CRP) biomarkers. Articles were assigned three possible values: '+1' if they significantly increase pro-inflammatory biomarkers or significantly decrease anti-inflammatory biomarkers; '-1' if they significantly increase anti-inflammatory biomarkers or significantly decrease pro-inflammatory biomarkers; and '0' if there is no significant changes in pro- or anti-inflammatory biomarkers (Shivappa et al., 2014). Next, manuscripts were weighted on the basis of the study design used. Then, the 'article effect score' was calculated by (1) dividing the weighted articles by the total number of weighted articles and (2) subtracting anti-inflammatory fractions from pro-inflammatory fractions. A representative composite database was then created to account for a wide range of dietary intakes worldwide. The dietary data for each individual was linked to the composite database in order to provide a robust estimate of the mean and standard deviations for each food parameter. Next, the "standard global mean" was subtracted from the reported intake and divided by the standard deviation to produce a z-score (Shivappa et al., 2014). Z-scores were then

converted to proportions and centered by doubling and subtracting 1 in order to avoid 'right skewing'. Centered-percentiles are then multiplied by the respective 'overall food parameter-specific inflammatory effect score' to estimate the 'food parameter-specific DII score'. These parameter-specific scores are then added together to calculate the 'overall DII score' (Shivappa et al., 2014).

Evidence shows that individuals who have higher energy intakes tend to consume more of every food parameter (pro- and anti-inflammatory). Furthermore, individuals who follow nutrient-dense or energy-dense dietary patterns ('healthy eater' or 'unhealthy eater', respectively) produce negative correlations between energy density and nutrient density (Darmon et al., 2005; Drewnowski & Fulgoni, 2014; Hébert et al., 2019). This realization led to the development of the E-DII. The E-DII assesses an individual's nutritional intake and adjusts per 1,000 calories consumed (Khan et al., 2018). An energy-adjusted composite database was needed to calculate E-DII scores. Both the DII and E-DII are scored and scaled similarly to allow for comparison across studies (Hébert et al., 2019). The E-DII showed a better model fit compared to the DII based on Akaike Information Criteria (AIC) (Portet, 2020). E-DII scores were calculated among SJLIFE participants based on 27 distinct macro- and micronutrients that were available. E-DII scores were calculated for each participant in this study, where a higher score is indicative of a pro-inflammatory diet (Shivappa et al., 2014).

Anxiety and Depression

Anxiety and depression symptoms can be determined through the use of self-report measures that assess the severity and whether individuals do or do not have anxiety and/or depressive symptoms (Zeltzer et al., 2009). The Brief Symptom Inventory is a 53-item

instrument that assesses a series of psychological symptoms (Grassi et al., 2018). The Brief Symptom Inventory-18 (BSI-18) is an 18-item self-report symptom checklist that was derived from the BSI to be an easy screening tool and to prevent an overload among patients (Franke et al., 2017). The BSI-18 specifically assesses anxiety, depressive symptoms, and somatic symptoms (Grassi et al., 2018; Zeltzer et al., 2009). The validity of the BSI-18 is supported through a 3-factor structure (i.e., anxiety, depression, and somatization) that was based on adult survivors of childhood cancer (Grassi et al., 2018; Recklitis et al., 2006), breast cancer (Galdón et al., 2008; Grassi et al., 2018), and pancreatic cancer patients (Clark et al., 2010; Grassi et al., 2018). The 18 items in the BSI-18 are rated on a 5-point scale assessing how much the specific symptom had bothered each participant in the prior week. Depression and anxiety each account for 6-items of the 18 total items. The remaining 6-items refer to symptoms of somatization (Grassi et al., 2018; Zeltzer et al., 2009). Raw scores are converted into t-scores. T-scores represent standardized normalizing transformations that reflect proportion (area) under the normal curve derived from that score. T-scores are then dichotomized with a clinically significant cut point of ≥ 63 as being sufficient to classify an individual as having psychological distress from the specific disorder (anxiety or depression) (Recklitis et al., 2017, 2006; Zeltzer et al., 2009). T-scores were analyzed as continuous and binary response variables for SJLIFE participants.

Covariates

Covariates that were considered for possible adjustment included demographic factors, lifestyle factors, and treatment factors. Demographic factors are age, gender, race, and education. Each participants' age at the time of their first visit was used. 'Race' was

divided into three categories: White, Black, or other. Education was separated into four categories: 1st-12th grade but did not graduate, high school (HS) diploma or GED, training after HS or some college, and college graduate. Lifestyle factors include smoking status, alcohol intake, and physical activity. Satisfying physical activity (PA) recommendations was determined based on the definition by the Center or Disease Control and Prevention (CDC) and the American College of Sports Medicine. This requires individuals to have at least 150 to 300 minutes of moderate PA a week, at least 75 to 150 minutes of vigorous PA a week, or an analogous combination of moderate and physical activity that results in a health benefit to the individual (Martin et al., 2000; Piercy et al., 2018). Smoking was dichotomized into ever smokers and never smokers. Ever-smokers were defined as individuals who have smoked a minimum of 100 cigarettes within their lifetime, a never smokers were defined as individuals who smoked less than 100 cigarettes throughout their lifetime (Cataldo et al., 2012). Heavy alcohol use was defined as consuming more than three drinks in a day for women and more than four drinks in a day for men based on the National Institute of Alcohol Abuse and Alcoholism (NIAAA) (Alcoholism, n.d.). Body Mass Index (BMI) is based on an individual's weight (kg) divided by their height (m^2). Individuals are considered underweight if they have a BMI less than 18 kg/m^2, normal weight if their BMI is between 18 and 25 kg/m^2, overweight if their BMI is between 25 and 29.9 kg/m^2, and obese if their BMI is above 30 kg/m^2 (Kramer et al., 2016). Due to the small number of underweight individuals, the categories for underweight and normal weight were combined. Treatments include radiation, and chemotherapy. Radiation therapy received during treatment for their diagnosis was categorized into 'cranial radiation', 'non-cranial radiation', and no radiation. The use of alkylating agents was

dichotomized as to whether they had (yes) or had not (no) received this form of chemotherapy for their diagnosis (Brinkman et al., 2018).

Statistical Analysis

The statistical software SAS 9.4 (SAS Institute, Cary, NC, USA) was used for all statistical analyses. Previous research investigating the association between diet-associated inflammation and mental health has categorized the DII or E-DII to compare the most anti-inflammatory diets and the most pro-inflammatory diets (Bergmans & Malecki, 2017; Ghazizadeh et al., 2020; C. M. Phillips et al., 2018b; Salari-Moghaddam, Keshteli, Afshar, Esmaillzadeh, & Adibi, 2019; Shakya et al., 2021; Shivappa, Hebert, & Rashidkhani, 2017; Shivappa, Hebert, et al., 2018; Wang et al., 2019). Therefore, the E-DII was divided into quartiles at the 25^{th}, 50^{th}, and 75^{th} percentiles for the total sample of survivors and controls. ANOVA or Kruskal-Wallis tests were used to estimate the means and standard deviations (SD) or medians and interquartile ranges (IQR) for continuous variables across E-DII quartiles. Chi-square tests were performed to estimate frequencies and percentages for categorical variables across E-DII quartiles. Multiple Imputation (MI) was used to address missing data on covariates. First, plausible values are generated (imputed) for missing data. Second, the data is analyzed for a set number of predetermined imputations (i.e., 100). Third, all generated imputations were combined into a single estimate. Since covariates with missing information (education, heavy drinking, and smoking) were binary/categorical predictors, fully conditional specification (FCS) was used for imputation. The FCS method allows for the imputation of binary and categorical variables. Furthermore, FCS is more flexible in its imputation estimates compared to other methods, such as the Multivariate normal imputation (MVNI) (Lee & Carlin, 2010; van Buuren,

2007). To investigate the association between anxiety and depression symptoms and the E-DII, both linear and logistic models were used in the analysis. Multivariable models assessing the association between the exposure (pro-inflammatory diet) and outcomes (anxiety and depressive symptoms) were adjusted for age, sex, race, education, BMI, smoker status, heavy drinking, meeting physical activity recommendations, cranial radiation, use of alkylating agents, and study population (survivor or control). Finally, multivariable models were stratified by sex to determine any significant differences between males and females as observed in previous research (Shakya et al., 2021). The E-DII was analyzed as a continuous variable and as a categorical (categorized into quartiles) predictor variable for both cancer survivors and controls overall. Significance was determined by p-values <0.05 for beta coefficients and 95% confidence intervals excluding the value '1' for ORs.

5.3 Results

A sample of 4,317 participants of the SJLIFE study (566 community controls and 3,751 survivors) who were treated for a pediatric malignancy between 1962 and 2012 were included in this study (Hudson et al., 2011). Descriptive statistics of the SJLIFE participants are presented across E-DII quartiles in Table 5-1. Participants in this study had a mean age of 30.8 ± 8.8 years. E-DII scores ranged from -5.84 to +4.57 among SJLIFE participants (survivors and community controls). E-DII quartiles ranged from -5.84 to -1.51 for quartile 1 (most anti-inflammatory), -1.51 to 0.46 for quartile 2, 0.46 to 1.87 for quartile 3, and 1.87 to 4.57 for quartile 4 (most pro-inflammatory). Among individuals in the highest quartile of the E-DII, the average age was 29.6 ± 8.4 years old. Participants in this quartile were more likely to be men, Black, less educated, ever smokers, heavy

drinkers, physically inactive, sarcoma or embryonal tumor survivors, and administered alkylating agents.

In the multivariable analysis, anxiety as a continuous variable showed that for every unit increase of the E-DII there was a non-significant decrease in t-score. The multivariable logistic regression with anxiety as a binary response showed that for every unit increase in E-DII the odds of anxiety had a non-significant decrease (Table 5-2). In the multivariable analysis, depression, fit as a continuous variable, showed that for every unit increase of the E-DII there was a nonsignificant decrease in t-score. The multivariable logistic regression with depression as a binary response showed that for every unit increase of the E-DII there was a 7% increase in the odds of depression ($\beta = 0.07$, 95% CI: [0.02, 0.12], p-value 0.01).

Anxiety was observed to have a non-significant negative association with the E-DII. Men were observed to have a non-significant negative association between the E-DII and anxiety. Women were observed to have a non-significant positive association between anxiety and E-DII scores. Depression was observed to have a significant positive association with the E-DII in the multivariable model combining both sexes (OR = 1.07, 95% CI: [1.02, 1.13]). However, the stratified analysis showed non-significant positive associations between depressive symptoms and E-DII scores among both men and women (Table 5-3). Table 5-4 presents the ORs and 95% CIs for the association between mental health outcomes and quartiles of the E-DII. Anxiety was observed to have non-significant positive associations with E-DII scores (Table 5-4). In contrast, depression was observed to have a significant positive association with E-DII scores comparing quartiles 2, 3, and 4 to quartile 1 that representing a consistent dose-response ($OR_{\text{Quartile 2vs1,}} = 1.43$, 95% CI:

[1.05, 1.95]; $OR_{Quartile\ 3vs1,}$ = 1.61, 95% CI: [1.19, 2.19]; $OR_{Quartile\ 4vs1,}$ = 1.63, 95% CI: [1.19, 2.23], respectively) in the fully adjusted model. Finally, Table 5-5 showed non-significant positive associations between anxiety and diet-associated inflammation, comparing quartile 4 to quartile 1 for both men and women. Among males, the logistic regression model assessing the association between depression and diet-associated inflammation showed a significant positive association comparing quartile 4 and quartile 1 ($OR_{Quartile\ 4vs1}$ = 1.94, 95% CI: [1.18, 3.18]). However, among women, the positive association was no longer significant when comparing quartile 4 to quartile 1 ($OR_{Quartile\ 4vs1}$ = 1.38, 95% CI: [0.89, 2.14]).

5.4 Discussion

Consistent with our hypothesis, SJLIFE participants who consumed pro-inflammatory diets were found to have a greater odds of depressive symptoms. This result remained consistent among men but not among women comparing the most anti-inflammatory diets and the most pro-inflammatory diets. Unlike depression, SJLIFE participants who consumed pro-inflammatory diets were not found to have a significant change in the odds of anxiety.

The analysis of the E-DII (predictor) and anxiety (response) showed a non-significant negative association in the SJLIFE population. This is inconsistent with results seen in some other studies (C. M. Phillips et al., 2018b; Salari-Moghaddam et al., 2019); however, the literature, in general, is equivocal on this relationship. In a study by Phillips et. al., individuals from the Cork and Kerry Diabetes and Heart Disease Study (Phase II) who consumed a pro-inflammatory diet were associated with an elevated risk of anxiety (OR = 1.60, 95% CI: [1.15, 2.24]). This study recruited who were 50-69 years old from a

primary care center in Ireland (C. M. Phillips et al., 2018b). This differs significantly from the mean age of SJLIFE participants (30.8 years old), a study that recruited American childhood cancer survivors. Another study by Salari-Moghaddam et Al., found that among a population of Iranian adults, the odds of anxiety was higher among individuals with higher DII scores (OR = 1.69, 95% CI: [1.07, 2.67]). Participants in this study adults working in 50 different healthcare centers were recruited (Salari-Moghaddam et al., 2019). These workers, employed at healthcare centers, may have been more likely to consume an anti-inflammatory diet and less likely to consume foods that produce a pro-inflammatory effect. In contrast, some studies found results consistent with our finding that suggest the DII did not significantly predict anxiety in the SJLIFE cohort. A study by Ghazizadeh et al., reported that anxiety was not associated with a pro-inflammatory diet among males or females from the Mashad Stroke and Heart Atherosclerotic disorder (MASHAD) Study ($OR_{\text{Quartile 4vs1,}} = 1.21$, 95% CI: [0.78, 1.87]; $OR_{\text{Quartile 4vs1,}} = 1.33$, 95% CI: [1.00, 1.78], respectively). Participants recruited into the study had age ranges between 35-65 years old. Additionally, this study used different tools to assess symptoms of anxiety and depression. The Beck Anxiety Inventory (BAI) was used to evaluate anxiety and the Beck Depression Inventory II (BDI-II) was used to evaluate depression (Ghazizadeh et al., 2020). Furthermore, a study by Polanska et al., evaluating anxiety from individuals participating in population-based cohorts of the ALPHABET consortium observed a significant negative association between anxiety and E-DII scores (OR = 0.97, 95% CI: [0.94, 0.99]). However, this study assessed symptoms of anxiety and depression in children from four European countries (England, France, Netherlands, and Poland) based on their mother's E-DII score during pregnancy (Polanska et al., 2021).

The results for the association between depressive symptoms and the E-DII were overall consistent with previous studies. In a study by Phillips et. al., higher E-DII scores were significantly associated with an elevated risk of depressive symptoms after adjusting for age, BMI, PA, smoking, and alcohol consumption (OR = 2.23, 95% CI: [1.15, 4.36]) (C. M. Phillips et al., 2018b). Another study among US adults from NHANES reported that individuals in higher DII quartiles (3 and 4) had a significantly higher risk of depression compared to individuals in quartile 1 ($OR_{Quartile\ 3vs1,}$ = 1.41, 95% CI: [1.04, 1.92]; $OR_{Quartile\ 4vs1,}$ = 1.74, 95% CI: [1.25, 2.42], respectively) (Jorgensen, White, Sekikawa, & Gianaros, 2018). Furthermore, a meta-analysis by Wang et. al., investigating the association between diet-associated inflammation and depressive symptoms found an increased risk or odds of depressive symptoms in 6 observational studies (Wang et al., 2019). These studies ranged from the populations in the United States, Spain, Australia, France, and Ireland. The meta-analysis that estimated the pooled risk ratio for prospective and cross-sectional studies observed that overall a pro-inflammatory diet was associated with an increased risk of depression (OR = 1.23, 95% CI: [1.12, 1.35]) (Wang et al., 2019). Specifically, two studies from the meta-analysis were carried out in the United States that used data from the National Health and Nutrition Examination Survey (NHANES) (M. D. Wirth, Shivappa, Burch, Hurley, & Hebert, 2017), and the Osteoarthritis Initiative (OAI) (Shivappa, Hébert, et al., 2018). However, since 2018, more recent studies on the DII and depressive symptoms were published in 2020 and 2021. A study by Moludi et al., assessing depression in women aged 35-65 from Western Iran reported that a pro-inflammatory diet was associated with higher risk of depression compared to an anti-inflammatory diet (OR = 1.63, 95% CI: [1.1, 2.4]) (Moludi et al., 2020). Another study investigated the association

between a pro-inflammatory diet and depression among Australian adults from the North West Adelaide Health Study (NWAHS) using the Centre for Epidemiological Studies Depression Scale (CES-D). The results showed that a pro-inflammatory diet was associated with an increased odds of reporting depressive symptoms (Shakya et al., 2021).

Interestingly, the study by Shivappa et al. found that among women, a pro-inflammatory diet was significantly associated with depressive symptoms; however, the association was not statistically significant in men (Shivappa, Hébert, et al., 2018). Furthermore, the study among a sub-sample of adults from the MASHAD study found that among women with dietary practices in the upper quartiles of the DII there was statistically significant increased odds of depressive symptoms (OR = 1.37, 95% CI: [1.03, 1.83]) (Ghazizadeh et al., 2020). Another study by Phillips et al. further supported this and found that among women the risk of depression was higher among those who consume pro-inflammatory diets (OR = 2.29, 95% CI: [1.49, 3.51], p-value <.0001) (C. M. Phillips et al., 2018b). These finding are inconsistent with our study results since only men had a significant association between depression and pro-inflammatory E-DII scores. Furthermore, our results show a non-significant association between the E-DII and depression among women comparing the most anti-inflammatory and most pro-inflammatory diets. Differences observed between the study by Shivappa et al. and this study may have been due to differences in scales used to diagnose depressive symptoms, age distribution, and gender distribution. The mean age across tertiles in this study was approximately 60 years old (Shivappa, Hébert, et al., 2018); in contrast, the mean age in our study was approximately 30 years old for each quartile. The tool used to evaluate symptoms of anxiety and depression was the CES-D. Finally, our study had a majority of

male participants (51%) while the study by Shivappa et al. had a majority of female participants (51%) (Shivappa, Hébert, et al., 2018). The MASHAD study exclusively had participants that were between 35 and 65 years old; SJLIFE participants in this study ranged from 18 to 70 years old (Ghazizadeh et al., 2020). The study by Phillips et al., had a mean age of approximately 60 years for each tertile of the E-DII; while our study had an mean age closer to 30 years old for each quartile (C. M. Phillips et al., 2018b). Finally, another study by Wirth et al., evaluated the odds of depressive symptoms using the Patient Health Questionnaire-9 (PHQ-9) among a US representative sample from NHANES. Results from this study showed that a pro-inflammatory diet was associated with depressive symptoms in women but not men (M. D. Wirth, Shivappa, Burch, et al., 2017).

Strengths of this study include: 1) the ability to investigate associations in a large cohort of childhood cancer survivors; 2) the robust characterization of cancer-, health behavior-, and treatment-related exposures (Howell et al., 2020); and 3) the use of a validated tool (BSI-18) to assess anxiety and depressive symptoms in cancer survivors (Recklitis et al., 2017, 2006). Despite its strengths, this study is limited by the use of FFQ methodology, selection of participants, and the cross-sectional nature of the study. A study aimed at validating the use of FFQs in assessing dietary intakes of childhood cancer survivors found that intake is grossly underreported (F. F. Zhang, Roberts, et al., 2015). Social desirability may be playing a role in the underreporting observed by these survivors (F. F. Zhang, Roberts, et al., 2015). Social desirability refers to "the tendency to give answers that make the respondent good", such as underreporting dietary intake (Perinelli & Gremigni, 2016). However, we had no information on social desirability or another important response set, social approval. Another limitation is the selection of participants

for the study. First, individuals participating in the SJLIFE study may not be representative of childhood cancer survivors in the general population (Ness, Leisenring, Goodman, et al., 2009). Second, we had to limit the study to a sub-sample of the SJLIFE cohort that had available dietary intake information and psychological distress information. Finally, since both the E-DII scores and BSI-18 scores were analyzed cross-sectionally, it is possible that symptoms of anxiety and depression may precede the consumption of a pro-inflammatory diet. This would violate the temporal relationship between a pro-inflammatory diet and symptoms of anxiety and depression.

In conclusion, we found that the E-DII was able to significantly predict the odds of depression but not anxiety. Interventions are needed to improve the dietary practices of childhood cancer survivors (F. Zhang et al., 2015). The E-DII can be used as a tool to inform intervention strategies. Further research is needed to understand the complexity of this association, including the mechanism related to disease etiology. This study can promote the further investigation on the impact of dietary inflammation on mental health outcomes to fill the knowledge gap in this vulnerable population.

Table 5-1. Distribution of characteristics across E-DII quartiles, SJLIFE, United States 2007-2012

E-DII Quartile	Quartile 1 (-5.844, -1.506)	Quartile 2 (-1.506, 0.456)	Quartile 3 (0.456, 1.870)	Quartile 4 (1.870, 4.569)	
Characteristics	(N = 1080)	(N = 1079)	(N = 1079)	(N = 1079)	p-value [a,b]
Study Population					<.0001
Survivor	883 (82%)	934 (87%)	964 (89%)	970 (90%)	
Control	197 (18%)	145 (13%)	115 (11%)	109 (10%)	
Age (years)	32.1 ± 9.0	30.9 ± 8.7	30.8 ± 9.0	29.6 ± 8.4	<.0001
Sex					<.0001
Male	384 (36%)	540 (50%)	599 (56%)	687 (64%)	
Female	696 (64%)	539 (50%)	480 (44%)	392 (36%)	
Race/Ethnicity					<.0001
White	948 (88%)	901 (84%)	898 (83%)	872 (81%)	
Black	91 (8%)	145 (13%)	162 (15%)	189 (18%)	
Other	41 (4%)	33 (3%)	19 (2%)	18 (2%)	
Education					<.0001
0-12 Grade, did not graduate	33 (3%)	73 (7%)	107 (11%)	144 (14%)	
HS Diploma or GED	110 (11%)	178 (17%)	209 (21%)	292 (29%)	
Some College or Training	288 (29%)	359 (35%)	286 (39%)	391 (39%)	
College Graduate	565 (57%)	409 (40%)	293 (29%)	182 (18%)	
BMI (kg/m)					<.0001
<25	486 (45%)	416 (39%)	397 (37%)	465 (43%)	
25-29	307 (28%)	308 (29%)	347 (32%)	266 (25%)	
≥30	287 (27%)	355 (33%)	335 (31%)	348 (32%)	
Smoking					<.0001
Ever Smokers	233 (22%)	285 (26%)	332 (31%)	412 (38%)	
Never Smokers	843 (78%)	788 (74%)	740 (69%)	658 (62%)	
Heavy Drinking					<0.001
Yes	51 (5%)	64 (6%)	104 (10%)	99 (9%)	
No	1015 (95%)	999 (94%)	943 (90%)	950 (91%)	
Binge Drinking					0.01
Yes	537 (50%)	475 (44%)	539 (51%)	552 (52%)	
No	535 (50%)	594 (56%)	527 (49%)	513 (48%)	
Physical Activity					<.0001
Meets CDC	730 (68%)	579 (54%)	529 (49%)	490 (45%)	
Does not meet CDC	350 (32%)	500 (46%)	550 (51%)	589 (55%)	
Type of Cancer					<.0001
ALL	260 (24%)	308 (29%)	292 (27%)	270 (25%)	
CNS Tumors	89 (8%)	122 (11%)	158 (15%)	130 (12%)	

Hodgkin Lymphoma	136 (13%)	103 (10%)	103 (10%)	106 (10%)	
Sarcomas	98 (9%)	125 (12%)	121 (11%)	139 (13%)	
Embryonal Tumors	108 (10%)	102 (10%)	109 (10%)	149 (14%)	
Other	190 (18%)	172 (16%)	180 (17%)	174 (16%)	
No cancer	199 (18%)	147 (14%)	116 (11%)	111 (10%)	
Radiation					0.01
Cranial	203 (19%)	241 (22%)	260 (24%)	206 (19%)	
Non-cranial	306 (28%)	276 (26%)	302 (28%)	327 (30%)	
None	571 (53%)	562 (52%)	517 (48%)	546 (51%)	
Alkylating Agent					0.01
Yes	541 (50%)	605 (56%)	585 (54%)	618 (57%)	
No	539 (50%)	474 (44%)	494 (46%)	461 (43%)	

Data presented are Mean ± SD, N (%).

[a] Continuous Variables were compared using ANOVA

[b] Categorical Variables were compared using Chi-square test

Table 5-2. Beta estimates and confidence intervals for the association between E-DII, fit as continuous, and Mental Health outcomes, SJLIFE, United States 2007-2012

	Model 1[a]		Model 2[b]		Model 3[c]	
	B (95% CI)	P-value	B (95% CI)	P-value	B (95% CI)	P-value
Anxiety (t-score)	**0.15 (0.01, 0.29)**	**0.04**	**0.20 (0.06, 0.35)**	**0.01**	-0.03 (-0.19, 0.13)	0.74
Anxiety (binary)						
< 63	ref		ref		ref	
≥ 63	**0.06 (0.01, 0.10)**	**0.01**	**0.07 (0.02, 0.12)**	**0.003**	-0.01 (-0.06, 0.05)	0.82
Depression (t-score)	**0.46 (0.32, 0.60)**	**<.0001**	**0.49 (0.35, 0.63)**	**<.0001**	0.12 (-0.04, 0.27)	0.15
Depression (binary)						
< 63	ref		ref		ref	
≥ 63	**0.14 (0.10, 0.18)**	**<.0001**	**0.15 (0.11, 0.19)**	**<.0001**	**0.07 (0.02, 0.12)**	**0.01**

Data presented are β (95% CI).

[a] Unadjusted Model

[b] Age-adjusted Model

[c] Multivariable Model: adjusted for age, gender, race, education, BMI, smoking , heavy drinking, physical activity, cranial radiation therapy, alkylating agents, and study population (survivor/control). E-DII, Energy-adjusted Dietary Inflammatory Index;

Table 5-3. Crude and Sex-Stratified associations of the E-DII (continuous) with mental health outcomes, SJLIFE, United States 2007-2012

		Gender	
	Both Sexes[a]	Male[b]	Female[b]
Anxiety			
< 63	ref	ref	ref
≥ 63	0.99 (0.94, 1.05)	0.96 (0.89, 1.04)	1.02 (0.95, 1.19)
Depression			
< 63	ref	ref	ref
≥ 63	**1.07 (1.02, 1.13)**	1.07 (0.996, 1.15)	1.07 (0.993, 1.15)

Data are presented as ORs (95% CIs).

[a] Multivariable Model: adjusted for age, gender, race, education, BMI, smoking , heavy drinking, physical activity, cranial radiation therapy, alkylating agents, and study population (survivor/control).

[b] Multivariable Model: adjusted for age, race, education, BMI, smoking , heavy drinking, physical activity, cranial radiation therapy, alkylating agents, and study population (survivor/control). E-DII, Energy-adjusted Dietary Inflammatory Index;

Table 5-4. Odds Ratios and confidence intervals for the association between E-DII Quartiles and Mental Health Outcomes, SJLIFE, United States 2007-2012

	E-DII Quartile			
	Quartile 1 (-5.844, -1.499)	Quartile 2 (-1.499, 0.458)	Quartile 3 (0.458, 1.885)	Quartile 4 (1.885, 4.569)
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Anxiety (reference <63) [a]				
≥ 63	1 (ref)	1.08 (0.79, 1.49)	1.17 (0.85, 1.60)	1.09 (0.78, 1.50)
Depression (reference <63) [a]				
≥ 63	1 (ref)	**1.43 (1.05, 1.95)**	**1.61 (1.19, 2.19)**	**1.63 (1.19, 2.23)**

Data are presented as ORs (95% CIs).

[a] Multivariable Model: adjusted for age, gender, race, education, BMI, smoking , heavy drinking, physical activity, cranial radiation therapy, alkylating agents, and study population (survivor/control). E-DII, Energy-adjusted Dietary Inflammatory Index;

Table 5-5. Sex-stratified Odds Ratios and confidence intervals for the association between E-DII Quartiles and Mental Health Outcomes, SJLIFE, United States 2007-2012

	E-DII Quartile			
	Quartile 1 (-5.844, -1.499)	Quartile 2 (-1.499, 0.458)	Quartile 3 (0.458, 1.885)	Quartile 4 (1.885, 4.569)
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Male [a]				
Anxiety (reference <63)				
≥ 63	1 (ref)	1.16 (0.70, 1.92)	1.05 (0.63, 1.74)	1.01 (0.61, 1.66)
Depression (reference <63)				
≥ 63	1 (ref)	**1.77 (1.07, 2.94)**	**1.76 (1.06, 2.90)**	**1.94 (1.18, 3.18)**
Female [a]				
Anxiety (reference <63)				
≥ 63	1 (ref)	0.98 (0.65, 1.49)	1.28 (0.85, 1.93)	1.15 (0.73, 1.80)
Depression (reference <63)				
≥ 63	1 (ref)	1.19 (0.79, 1.78)	**1.59 (1.06, 2.38)**	1.38 (0.89, 2.14)

Data are presented as ORs (95% CIs).

[a] Multivariable Model: adjusted for age, race, education, BMI, smoking , heavy drinking, physical activity, cranial radiation therapy, alkylating agents, and study population (survivor/control). E-DII, Energy-adjusted Dietary Inflammatory Index

CHAPTER 6

THE ENERGY-ADJUSTED DIETARY INFLAMMATORY INDEX (EDII) AND CARDIOVASCULAR DISEASE (CVD) AMONG CHILDHOOD CANCER SURVIVORS (CCS): THE ST. JUDE LIFETIME COHORT STUDY (SJLIFE)

Abstract

Introduction: Cardiovascular disease (CVD) represents a common and serious set of comorbidities among adult survivors of childhood cancer. CVDs are known to be associated with chronic, systemic inflammation and diet is an important modulator of inflammation. We investigated the association between the Energy-adjusted Dietary Inflammatory Index (E-DII™) score, as an indicator of diet-associated inflammation (higher E-DII scores indicate a more pro-inflammatory diet), and CVD outcomes in a cohort of childhood cancer survivors.

Methods: Data were from participants in the St. Jude Lifetime Cohort Study (SJLIFE), a retrospective hospital-based study with prospective follow-up on childhood cancer survivors treated at St. Jude Children's Research Hospital (SJCRH). Dietary information on SJLIFE participants was collected using the 2005 Block Food Frequency Questionnaire (FFQ). This study was restricted to SJLIFE participants that had available dietary information. Diet-associated inflammation, a measure of dietary quality, was assessed using the E-DII, calculated per 1000 kcal of foods consumed. Several CVD-related

outcomes were identified among SJLIFE participants including hypertension (140 mm Hg and/or a diastolic blood pressure of 90 mm Hg), hyperlipidemia (hypertriglyceridemia >100 mg/dL and/or hypercholesterolemia ≥200 mg/dL), cardiomyopathy (systolic ejection fraction <50%), coronary artery disease (CAD) (history of myocardial infarction, wall motion defect, and/or ischemia), cardiac dysrhythmia (detection of rhythm abnormality), and cerebrovascular accidents (CVA) (ICD-9/10 codes). Unadjusted, age-adjusted, and multivariable logistic regression models were fit to analyze the potential association of E-DII scores and CVD-related events (Yes/No). Logistic regression models were fit using E-DII scores as a continuous and as categorical (quartiles) predictors. Multivariable models were adjusted for age, gender, race, education, BMI, smoking, heavy drinking, physical activity (PA), and survivor status (survivor or control). In addition, some models were adjusted for alkylating agents (hypertension and hyperlipidemia), anthracyclines (cardiomyopathy), antimetabolites (hypertension), chest radiation (hypertension, hyperlipidemia, cardiomyopathy, and cardiac dysrhythmia), cranial radiation (CVA), hypertension status (CAD and cardiac dysrhythmia), and hyperlipidemia status (CAD). Covariates were selected using 'disjunctive causal criterion'. Finally, analyses were stratified by sex. SAS 9.4 (SAS Institute, Cary, NC, USA) were used for all statistical analyses.

Results: There were 4,520 participants with evaluable data (2,331 men and 2,189 women). The mean age was 30.7 ± 8.8 years old in the overall study sample. E-DII scores among SJLIFE participants ranged from -5.84 to 4.57. The age-adjusted models analyzing the E-DII as quartiles showed a pro-inflammatory diet had statistically significant positive association with hypertension. In contrast, the E-DII as a continuous predictor was shown

to have significant negative associations with Hyperlipidemia in the age-adjusted model. The E-DII categorized into quartiles showed a nonsignificant negative association with hyperlipidemia. CAD was associated with the E-DII (continuous) in the age-adjusted model. The E-DII as a categorical predictor had a significant positive association with CAD in the unadjusted, age-adjusted, and multivariable models. In the multivariable model, quartile 3 was observed to have a higher odds of CAD compared to individuals in the first quartile ($OR_{Quartile3vs1,}$ = 1.34, 95% CI: [1.003, 1.80]). However, comparing quartile 4 to quartile 1 no association was observed ($OR_{Quartile4vs1,}$ = 0.99, 95% CI: [0.72, 1.38]). The logistic regression model assessing the association between E-DII scores and cerebrovascular accidents produced a significant positive association in the unadjusted and age-adjusted models (Unadjusted: $OR_{Quartile\ 2vs1}$ = 2.32, 95% CI: [1.23, 4.38]; $OR_{Quartile\ 3vs1}$ = 2.10, 95% CI: [1.10, 4.00]; Age-adjusted: $OR_{Quartile\ 2vs1}$ = 2.36, 95% CI: [1.26, 4.46]; $OR_{Quartile\ 3vs1}$ = 2.15, 95% CI: [1.13, 4.09]). However, no significant relationships were observed in the multivariable model. No significant associations were observed between E-DII scores (continuous and categorical) and cardiomyopathy or cardiac dysrhythmia. Stratified analysis showed that women in quartile 2 had a higher odds of CVA compared to women in quartile 1 ($OR_{Quartile2vs1,}$ = 5.71, 95% CI: [1.86, 17.33]). The strength of the association decreased with increasing quartile, demonstrating the absence of a dose-response association.

Discussion: The results from this study indicate a diet consisting of high amounts of pro-inflammatory food parameters and low amounts of anti-inflammatory food parameters are inconsistently associated with an increased odds of hypertension, CAD, and CVA. In addition, results from this study indicate that pro-inflammatory diets are associated with a

decreased odds of hyperlipidemia. This result is counterintuitive to previous literature. Overall, our study results suggest that dietary inflammation may be useful in regulating hypertension, CAD, and CVA. Specifically, interventions promoting an anti-inflammatory diet may help regulate CVA among women.
Keywords: Cardiovascular Disease (CVD), inflammation, childhood cancer survivors, hypertension, hyperlipidemia, cardiomyopathy, Coronary Artery Disease (CAD), cardiac dysrhythmia, Cerebrovascular Accident (CVA).

6.1 Introduction

Advances in multimodal therapy to treat childhood cancer has led to an improved prognosis in childhood cancers survivors. Consequently, childhood cancers survivors now have a 5-year survival rate above 84% in the United States (Armstrong et al., 2016; Bethesda, 2015; Howell et al., 2020). Today, there are approximately half a million childhood cancer survivors living in the US (Armstrong et al., 2016; Y. Chen et al., 2020; Robison & Hudson, 2014). Unfortunately, treatments that improved their prognosis can also adversely affect the function of other organ systems (Bansal et al., 2020). Childhood cancer survivors remain at an elevated risk for recurrence and progression of their initial cancer and they are at an elevated risk for new malignancies, functional impairments, and chronic conditions (Armstrong et al., 2016; Cardous-Ubbink et al., 2004; Dowling et al., 2010; M. C. Hoffman et al., 2013; S. M. Phillips et al., 2015; Pui et al., 2003; Reulen et al., 2010; Robison & Hudson, 2014). Cardiovascular Disease (CVD) remains a major concern for childhood cancer survivors for the remainder of their lives (Armenian et al., 2018). Survivors of childhood malignancies are approximately seven times more likely than

individuals from the general population to die from a CVD-related event (Armenian et al., 2018).

Long-term follow up of childhood cancer survivors has received increased attention by researchers (J. E. Cohen, Wakefield, & Cohn, 2016). Prevention strategies aimed at improving the overall quality of life may be important to reducing the burden of chronic conditions among survivors (J. E. Cohen et al., 2016; J. Cohen et al., 2012). Specifically, lifestyle interventions may help manage the morbidity and mortality from CVD in this population. However, despite the evidence that healthy behaviors can decrease the impact of adverse chronic events, the prevalence of healthy behaviors in this group of survivors remains similar to the general population (J. E. Cohen et al., 2016). Dietary intake is among the few modifiable health behaviors that can prevent or delay the onset of chronic conditions, such as CVD (F. F. Zhang et al., 2016). Survivors of childhood malignancies, generally, do not meet dietary recommendations, consuming diets high in fat and low in fruit and vegetables (J. E. Cohen et al., 2016; Robien et al., 2008; F. F. Zhang et al., 2016; F. F. Zhang, Roberts, et al., 2015). Ten years ago, the then-available evidence indicated that dietary recommendations for childhood cancer survivors need to consider the impact of dietary intake on systemic inflammation (Galland, 2010). Inflammation can increase the risk of insulin resistance and atherosclerosis which are precursors to the development of subsequent CVD (Golia et al., 2014; Soysal, Arik, Smith, Jackson, & Isik, 2020).

Diet is an important regulator of systemic inflammation, which can be assessed through biologic markers, such as tumor necrosis factor-α (TNF- α) and high sensitivity C-reactive protein (hsCRP) (Mazidi et al., 2018). Observational studies have found associations between diet and these biomarkers. For example, the Mediterranean diet,

which is high in grains, fruits, and vegetables, and low in fat intake, especially saturated fatty acids, is associated with low levels of inflammatory biomarkers (e.g. hsCRP) (Estruch et al., 2006; Mazidi et al., 2018). The opposite is true for diets of poor quality, such as the Western diet (intake high in fat and refined grains) (Johansson-Persson et al., 2014; Mazidi et al., 2018). Diet-associated inflammation among childhood cancer survivors may influence CVD risk in this vulnerable population.

The Dietary Inflammatory Index (DII®) is a tool, first developed in 2009 and later updated in 2014, that scores the inflammatory potential of an individual's diet on a scale that ranges from maximally anti-inflammatory to maximally pro-inflammatory (Cavicchia et al., 2009; Khan et al., 2018; Mazidi et al., 2018; Shivappa et al., 2014). Scoring is based on an extensive literature review on the pro- and anti-inflammatory properties of several food parameters (Mazidi et al., 2018). The DII can be used in nutritional studies with available dietary information (Shivappa et al., 2014). Although over 100 articles, including 6 meta-analyses, have been published on the DII and cardiovascular disease, there are no studies looking at the association between the DII and CVD among childhood cancer survivors. The most recent meta-analysis that explored this association across 14 studies, found that among individuals consuming pro-inflammatory diets there was an elevated risk of CVD compared to individuals consuming anti-inflammatory diets (RR = 1.36, 95% CI: [1.19, 1.57]) (Shivappa, Godos, et al., 2018). The DII is an effective tool to quantify the inflammatory potential of diet in influencing risk of adverse CVD events among childhood cancer survivors. The role of diet-associated inflammation in CVD has never, to our knowledge, been investigated in a cohort of childhood cancer survivors. We predict that diet-associated inflammation, as indicated by higher E-DII scores, will have statistically

significant positive associations with CVD outcomes among a cohort of childhood cancer survivors.

6.2 Methods

Study Design

The St. Jude Lifetime Cohort Study (SJLIFE) is a retrospective hospital-based study with prospective follow-up in which information is collected on childhood cancer survivors treated at St. Jude's Children's Research Hospital (SJCRH) over a 50-year span (1962-2012) (Howell et al., 2020). Initially, the cohort included childhood cancer survivors who were at least 18 years old at the time of clinical evaluation, were treated at SJCRH, and had a minimum of 10-years of survival from their initial cancer diagnosis. In 2015, the inclusion criteria was modified to include survivors of any age who had a minimum of 5-year survival since their initial diagnosis, and who were diagnosed for a pediatric malignancy up until June 30, 2012 (Howell et al., 2020). Controls, who were frequency matched on age, sex, and race were recruited into the SJLIFE study. Participants were given the option of 3 levels of participation: (1) comprehensive evaluation at SJCRH, (2) local evaluation, or (3) completion of health surveys by mail or phone (Hudson et al., 2011). The SJLIFE study was approved by the SJCRH Institutional Review Board on April 25th, 2007.

Measures

SJLIFE participants completed five questionnaires (i.e., the home survey, the behavior survey, health habits survey, the women's/men's health survey, and the Block Food Frequency questionnaire). Diet was assessed using the 2005 Block Food Frequency Questionnaires (FFQ) (Block, Hartman, & Naughton, 1990). FFQ-derived information was used to compute the DII scores. CVD outcomes, and data on covariates were obtained from

SJLIFE in order to conduct a cross-sectional analysis of the effect of dietary inflammation on CVD outcomes. Outcomes used in this study were detected or present at the time survivors (and controls) completed the FFQ. The study sample was restricted to individuals from the SJLIFE study who had available FFQ information. Demographic and lifestyle behavior information was gathered from completed questionnaires. Treatment data was gathered through medical record abstraction (Howell et al., 2020).

Dietary Intake and the Dietary Inflammatory Index (DII®)

Dietary information was collected by having participants complete the Block FFQ (Block et al., 1990; Howell et al., 2020), which includes information on approximately 110 food items and nutrients consumed during the past year (F. F. Zhang et al., 2018). Data were processed by Block Dietary Data Systems to estimate the nutrient intake referencing food-composition values for nutrients from the USDA Food and Nutrient Database for Dietary Studies and a food list from National Health and Nutrition Examination Survey (NHANES) (F. F. Zhang et al., 2016). FFQ-obtained dietary information was used to calculate DII and Energy-adjusted DII (E-DII^{TM}) scores for participants in the SJLIFE study.

The DII is a tool created to measure the overall effect of diet on inflammation (Shivappa et al., 2014). The DII is a literature derived tool that scores dietary intake based on the availability of 45 food parameters (Shivappa et al., 2014). Information on these food parameters were gathered from a total of 1,943 articles related to the role of dietary items to inflammatory biomarkers: IL-1β, IL-4, IL-6, IL-10, TNF-a, and CRP (Cavicchia et al., 2009; Shivappa et al., 2014). Articles were assigned three possible values: '+1' if they significantly increase pro-inflammatory cytokines (IL-1β, IL-6, TNF-a or CRP) or decrease

anti-inflammatory cytokines (IL-4 or IL-10); '-1' if they significantly increase anti-inflammatory cytokines (IL-4 or IL-10) or decrease pro-inflammatory cytokines (IL-1β, IL-6, TNF-a or CRP); and '0' if no significant changes were observed (Shivappa et al., 2014). Next, articles were weighed based on their specific study design based on causal inference. The 'article effect score' was calculated by dividing the weighted articles by the total number of articles and then subtracting the anti-inflammatory fraction from the pro-inflammatory fraction. The DII was then standardized based on a composite database on wide-ranging diets across several distinct populations around the globe (USA, Australia, Bahrain, Denmark, India, Japan, New Zealand, Taiwan, South Korea, Mexico, and the UK). Robust estimates of the means and standard deviations of each food parameter was used to create a z-score by subtracting standard global mean from reported intake and dividing by the global database standard deviation. Z-scores were then converted to centered proportions to reduce the effect of 'right skewing'. To achieve more symmetrical distributions, each proportion score was doubled and then subtracted by '1'. Values were centered on 0 and bounded between -1 (maximally anti-inflammatory) and 1 (maximally pro-inflammatory) (Shivappa et al., 2014). The centered proportion was next multiplied by the 'overall food parameter-specific inflammatory effect score' to estimate the 'food parameter-specific DII score'. Finally, all parameter specific scores are summed to create the 'overall DII score' (Shivappa et al., 2014). An association was observed between the total energy intake and DII scores (Hébert et al., 2019; Khan et al., 2018). In order to control for the effect of variability among individuals in total energy intake, the E-DII was created to adjust for caloric content of the diet consumed using the 'nutrient density model'(i.e., amount per 1,000 kilocalories [kcal]) (Mazidi et al., 2018). Use of the E-DII was based on

the goodness of fit of each index using the Akaike Information Criterion (AIC). E-DII scores were calculated among SJLIFE participants based on 27 macro and micro-nutrients that were available. A higher E-DII score is indicative of a more pro-inflammatory diet.

Cardiovascular Disease (CVD) outcomes

We examined six CVD outcomes: 1) hypertension, 2) hyperlipidemia, 3) cardiomyopathy, 4) CAD, 5) cardiac dysrhythmia, and 6) CVA. All cardiovascular health conditions are graded and classified using the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE v4.03) (Bhakta et al., 2016; Hudson et al., 2017; Hudson, Ness, Gurney, Mulrooney, Chemaitilly, et al., 2013). Modifications to the CTCAE v4.03 was made in order to: 1) define how clinical data was utilized in severity grading, 2) define more conservative ranges to avoid overdiagnosis, and 3) to conform to clinical practice at SJCRH (Bhakta et al., 2016). Cardiovascular events were defined as being grade 2 or above. A description of CTCAE grading is in Table 6-1. Hypertension (grade 2) was defined as having systolic blood pressure (SBP) ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg and taking medication (Bhakta et al., 2016). Screening for hypertension was carried out by clinical staff after participants remained in a seated position for five-minutes of rest (Gibson et al., 2017). Three measurements were taken consecutively after one-minute intervals through the use of a sphygmomanometer (Gibson et al., 2017; Hudson, Ness, Gurney, Mulrooney, Chemiatilly, et al., 2013; Kibria et al., 2018). Hyperlipidemia (grade 2) was determined based on total cholesterol, triglycerides, LDL, and HDL among participants (hypertriglyceridemia >300 mg/dL and/or hypercholesterolemia ≥300 mg/dL) and taking medication. Screening for hyperlipidemia was done through the use of a fasting lipid panel (Hudson, Ness, Gurney, Mulrooney,

Chemiatilly, et al., 2013). Cardiomyopathy (grade 2) was identified as a systolic ejection fraction <50% on an echocardiogram (Mulrooney et al., 2016). CAD (grade 2) was defined as having abnormal cardiac enzymes and no evidence of ischemic changes on electrocardiogram (ECG) (Mulrooney et al., 2016). Cardiac dysrhythmia (grade 2) was determined by the detection of a rhythm abnormality on an ECG (Hudson, Ness, Gurney, Mulrooney, Chemiatilly, et al., 2013). Cerebrovascular accidents (including stroke) (grade 2) are considered moderate events. Other information on CVAs were identified through the use of the International Classification of Diseases (ICD-9), 9th revisions (ICD-9: 430-434, 436, 437, 438, and 444); ICD-10 codes were also used (diagnosis codes beginning with I63) (Chow et al., 2018; Hsieh et al., 2020).

Covariates/Potential Confounders and Effect Modifiers

Variables to consider and to adjust for include demographic factors, lifestyle factors, and treatment factors. Demographic factors include age, gender, race, and education. Age at the time of their first visit was used. 'Race' was divided into 3 categories: White, Black, or other. Education was split into 4 categories: 1st-12th grade but did not graduate, high school (HS) diploma or GED, training after HS or some college, and college graduate. Lifestyle factors include physical activity (PA), smoking status, and alcohol intake. Performing adequate PA was the determined based on the definition by the Center or Disease Control and Prevention (CDC) and the American College of Sports Medicine. This requires individuals to accumulate 150 to 300 minutes of moderate PA a week or 75 to 150 minutes of vigorous PA per week in order to achieve a health benefit (Martin et al., 2000; Piercy et al., 2018). An ever smoker is defined as a person who has smoked a minimum of 100 cigarettes throughout their lifetime, a never smoker is defined as a person

who smoked less than 100 cigarettes in their lifetime (Cataldo et al., 2012). Heavy alcohol use is defined as consuming more than 4 drinks in a day for men and more than 3 drinks in a day for women (Alcoholism, n.d.). Body Mass Index (BMI) is calculated based on an individual's weight in kilograms divided by their height in meters squared (kg/m^2) as is standard practice. Individuals are considered at underweight if BMI is <18 kg/m^2, normal weight if their BMI is between 18 kg/m^2 and 25 kg/m^2, overweight if their BMI is between 25 and 29.9 kg/m^2, and obese if their BMI is above 30 kg/m^2 (Kramer et al., 2016). However, the small proportion of underweight individuals led to the combination of underweight and normal weight individuals; resulting in 3 groups for the analysis. Treatments include radiation (cranial and chest), chemotherapy (alkylating agents, anthracyclines, and antimetabolites). Radiation therapy received during treatment for their diagnosis was determined for each participant (Howell et al., 2020). Cranial and chest radiation were dichotomized (Yes/No). Having received alkylating agents, antimetabolites, and anthracyclines were dichotomized (Yes/ No). Finally, survivor status will be used as a binary predictor (survivor or control).

Confounder Selection

Confounders were selected for inclusion in the multivariable models based on information found in previous literature related to dietary inflammation and CVD outcomes (Hudson, Ness, Gurney, Mulrooney, Chemiatilly, et al., 2013; Shivappa, Godos, et al., 2018), through a method called "disjunctive causal criterion". This method controls for covariates that are causally associated with the exposure, or the outcome, or both. This method does not require knowledge of the full underlying causal diagram regarding how each of the covariates is related to all of the other covariates. In addition, instrumental

variables are omitted from the model. Instrumental variables are causally related to the exposure but not to the outcome except through the exposure variable. Furthermore, any proxy for any unmeasured variables are included into the model (Vanderweele, 2021). This method was implemented for each of the six CVD outcomes in this study.

Data Exclusion and Imputation

There are a total of 5,756 participants in the SJLIFE study. Of the initial cohort, 4,520 individuals had available dietary information. Multiple imputation was used to estimate values for missing data among SJLIFE participants. Data missing included information on education, smoking status, and heavy drinking status. The first step involved generating plausible values (imputations) for missing values (education, smoking, and heavy drinking). The second step involved analyzing the data through a pre-determined number of imputations (100). The third step involved combining all generated imputations into a single estimate. Specifically, the fully conditional specification (FCS) approach to imputation was used. Furthermore, the FCS approach allows for imputation of binary and categorical variables. FCS is a more flexible method of imputation compared to other methods, such as Multivariate normal imputation (MVNI) (Lee & Carlin, 2010; van Buuren, 2007). Following imputation, 4,520 individuals (3,932 survivors and 588 controls) were retained into the study sample (Figure 6-1).

Statistical Analysis

The statistical software SAS 9.4 (SAS Institute, Cary, NC, USA) was used for all statistical analyses. The E-DII was used as a continuous variable and categorized into quartiles for the analysis, with quartile 4 being the most pro-inflammatory and quartile 1 being the most anti-inflammatory. Age is the only continuous variable used in this study

and it was not normally distributed. Due to this, a Kruskal-Wallis test was used to compare age across E-DII quartiles (Ghazizadeh et al., 2020). The median and interquartile range (IQR) for 'age' were estimated for each E-DII quartile. Chi-square tests were performed to estimate frequencies and percentages for comparison of categorical variables across E-DII quartiles.

To investigate the association between CVD outcomes and the E-DII, both linear and logistic models were used in the analysis. Multivariable analyses were carried out adjusting for covariates specific to each outcome. All multivariable models were adjusted for age, sex, race, education, body mass index (BMI), ever/never smoker status, heavy drinking, meeting physical activity (PA) recommendations, and survivor status. Multivariable analysis on hypertension was also adjusted for alkylating agents, antimetabolites, and chest radiation. Multivariable analysis on hyperlipidemia was also adjusted for alkylating agents, and chest radiation. Multivariable analysis on cardiomyopathy was also adjusted for anthracyclines, and chest radiation. Multivariable analysis on Coronary Artery Disease (CAD) was also adjusted for hypertension status, and hyperlipidemia status. Multivariable analysis on cardiac dysrhythmia was also adjusted for chest radiation, and hypertension status. Multivariable analysis on Cerebrovascular Accident (CVA) was also adjusted for cranial radiation. Finally, analyses were also performed on each CVD outcomes that was stratified by sex.

6.3 Results

There were 4,520 participants with evaluable data (2,331 men and 2,189 women). The mean age was 30.7 ± 8.8 years old in the overall study sample. E-DII scores ranged from -5.84 to 4.57. Table 1 shows the characteristics of SJLIFE participants across quartiles

of the E-DII scores. Age decreased with increasing E-DII scores. Individuals in quartile 4 were more likely to be males, Black, less educated, obese, ever smokers, heavy drinkers, binge drinkers, physically inactive (based on CDC recommendations), survivors of sarcomas and embryonal tumors, and hypertensive compared to individuals in E-DII quartile 1.

Analysis of Hypertension

Results from the logistic regression model assessing the odds of having hypertension show nonsignificant positive associations between the E-DII as a continuous score and hypertension status in the unadjusted, and multivariable models (Table 6-3). However, the age-adjusted model showed a significant positive association between E-DII as a continuous predictor and hypertension ($OR_{age\text{-}adjusted}$ = 1.06, 95% CI: [1.03, 1.10]). Furthermore, the age-adjusted model comparing quartile 4 to quartile 1 showed a significant positive association between the E-DII and hypertension status ($E\text{-}DII_{Quartile\ 4\ vs\ 1,}$ OR = 1.46, 95% CI: [1.17, 1.81]). No significant association was seen between the E-DII score and hypertension in the unadjusted and multivariable models comparing E-DII quartiles 2, 3, and 4 to quartile 1 (Table 6-3).

Analysis of Hyperlipidemia

Results of the logistic regression model assessing the odds of having hyperlipidemia showed significant negative associations between the E-DII as a continuous variable and hyperlipidemia status only in multivariable model ($OR_{Multivariable}$ = 0.91; 95% CI: [0.86, 0.97]). In addition, logistic regression models showed no association between the E-DII and hyperlipidemia in all 3 models comparing quartile 4 to quartile 1.

Specifically, in the multivariable model, E-DII quartiles 2, 3, and 4 there was no association with hyperlipidemia when compared to individuals in quartile 1.

Analysis of Cardiomyopathy

Results of the logistic regression models assessing the odds of having cardiomyopathy showed no associations between the E-DII as both a continuous variable and as quartiles with cardiomyopathy status (Table 6-4).

Analysis of Coronary Artery Disease (CAD)

Results of the logistic regression model assessing the odds of having CAD showed a significant positive association between the E-DII as a continuous variable and CAD status in the age-adjusted model ($OR_{Age\text{-}adjusted}$ = 1.14, 95% CI: [1.05, 1.24]). In the age-adjusted model of the E-DII categorized, quartiles 2, 3, and 4 had a significant positive association with CAD when compared to quartile 1 ($OR_{Quartile\ 2vs1,}$ = 1.85, 95% CI: [1.10, 3.10]; $OR_{Quartile\ 3vs1,}$ = 2.30, 95% CI: [1.39, 3.84]; $OR_{Quartile\ 4vs1,}$ = 1.97, 95% CI: [1.16, 3.35]). In the multivariable model, E-DII quartiles 3 had a significant positive association with CAD when compared to quartile 1 ($OR_{Quartile\ 3vs1,}$ = 1.34, 95% CI: [1.003, 1.80]).

Analysis of Cardiac Dysrhythmia

Results of the logistic regression model assessing the odds of having cardiac dysrhythmia show nonsignificant associations between the E-DII as both a continuous and categorical variable with cardiac dysrhythmia. In the unadjusted and age-adjusted models, the E-DII shows nonsignificant negative associations with dysrhythmia (Table 6-7). In contrast, the multivariable model showed a nonsignificant positive association with dysrhythmia. The logistic regression models using E-DII quartiles as the main predictor show similar inconsistencies. In the unadjusted and age-adjusted model, comparison of

quartiles 4 and 1 show nonsignificant negative associations with the dysrhythmia. In the multivariable model, quartile 4 showed nonsignificant negative association with cardiac dysrhythmia when compared to quartile 1. In contrast, quartile 3 shows a nonsignificant positive association with cardiac dysrhythmia when compared to quartile 1.

Analysis of Cerebrovascular Accidents (CVA)

Results from the logistic regression assessing the odds of having a CVA shows nonsignificant positive associations between the E-DII as a continuous variable and CVA events (Table 6-7). The logistic regression models using E-DII quartiles showed significant positive associations in the unadjusted and age-adjusted models. In the unadjusted model, quartiles 2 and 3 were associated with an increased odds of CVA compared to quartile 1 (Table 6-8). However, comparison of quartiles 4 and 1 showed a nonsignificant positive association with CVA. In the age-adjusted model, quartiles 2 and 3 were also associated with an increased odds of CVA compared to quartile 1 ($OR_{\text{Quartile 2vs1,}} = 2.36$, 95% CI: [1.26, 4.46]; $OR_{\text{Quartile 3vs1,}} = 2.15$, 95% CI: [1.13, 4.09]). However, comparing quartile 4 to quartile 1, a nonsignificant positive association was observed between the E-DII and CVA (Table 6-8). No significant association were observed between the E-DII quartiles and CVA in the multivariable models.

Analysis of CVD outcomes Stratified by Sex

Logistic regression assessing the sex-stratified associations between CVD outcomes and quartiles of the E-DII are presented in Table 6-9. There were no significant associations between E-DII score and hypertension, hyperlipidemia, cardiomyopathy, CAD, and cardiac dysrhythmia in the sex-stratified analysis. However, a significant positive association was observed between CVA and E-DII scores among women in

quartile 2 compared to females in quartile 1 ($OR_{Quartile\ 2vs1,} = 5.71$, 95% CI: [1.86, 17.53]). However, a nonsignificant positive association was observed comparing women in quartile 4 to women in quartile 1.

6.4 Discussion

The results from this study indicate that a pro-inflammatory diet, as indicated by the E-DII, may be significantly associated with an increased odds of hypertension, CAD, and CVA among survivors and controls. However, these associations are considered to be inconsistent in this study. For hypertension, ORs tend to increase with increasing quartiles of the E-DII in a dose-response manner. In contrast, CAD and CVA were observed to have increasing ORs comparing quartiles 2 and 3 to quartile 1. However, when comparing quartile 4 to quartile 1, the odds of CAD and CVA tend to decrease from values observed comparing quartile 3 to quartile 1. In addition, results from this study indicate that pro-inflammatory diets are associated with a decreased odds of hyperlipidemia. Overall, most of our study results are inconsistent with the hypothesis that dietary inflammation is predictive of certain CVD outcomes. To our knowledge, this is the first study to assess the role of dietary inflammation on the occurrence of adverse CVD events among childhood cancer survivors. Although other studies have already looked at the impact of diet quality in this population, the inflammatory potential of dietary intake has never been considered in regards to intervention strategies aimed at reducing the burden of CVD in childhood cancer survivors (Belle et al., 2017; Berdan et al., 2014; J. Cohen et al., 2012; Robien et al., 2008; Stolley et al., 2010; Teixeira et al., 2018; F. F. Zhang, Roberts, et al., 2015).

E-DII scores were associated with an increased odds of hypertension. This is consistent with other studies assessing various dietary indexes, such as the Mediterranean

diet, that indicates diet quality can predict the development of hypertension. A review of the literature by Pergola et. al., found that the consuming a Mediterranean diet, which contains nutrient-dense foods (e.g., whole grains, vegetables, fruits, and nuts) reduces the risk of hypertension (De Pergola & D'alessandro, 2018). A study by Hodge et al., showed that the Mediterranean Diet and an anti-inflammatory diet were associated with lower CVD mortality; both types of diets showed very similar associations (Hodge et al., 2018). Furthermore, the E-DII has been observed to be associated with an increased odds of CAD among the SJLIFE participants. Similar results were observed in a study by Agraib et. al., which found that among Jordanians there was an excess risk of CAD among individuals consuming a pro-inflammatory diets (Agraib et al., 2019). Pro-inflammatory E-DII scores are associated with an increased odds of CVA. This is consistent with other literature that has observed that energy-dense diets (pro-inflammatory), such as a 'Western diet', increases risk of stroke (Boden-Albala, Southwick, & Carman, 2015; Boehme, Esenwa, & Elkind, 2017). Nutrient-dense diets, such as the Mediterranean diet, have been reported to aid in reducing the risk of CVAs, such as stroke (Boehme et al., 2017). Diet is an important regulator of the risk of CVA and other CVD outcomes, such as hypertension and dyslipidemia (Boehme et al., 2017). A meta-analysis by Feng et al., found that among 12 prospective studies, higher adherence to the Dietary Approaches to Stop Hypertension (DASH) diet was associated with a reduced risk of a stroke event. However, this association appeared to be stronger among Asian populations compared to Western populations. Specifically, a linear association was observed between the DASH diet score and stroke risk (Feng et al., 2018). A recent study has reported the DASH diet is associated

with a decrease the inflammatory biomarker, high sensitivity C-reactive protein (hs-CRP) (Soltani, Chitsazi, & Salehi-Abargouei, 2018).

Our study indicates that a pro-inflammatory diet is negatively associated with hyperlipidemia. This is inconsistent with previous literature that observed an energy-dense, nutrient sparse diets with high intake of total cholesterol, LDL cholesterol, and triglycerides increase the risk of dyslipidemia. Generally, a decreased risk of hyperlipidemia is associated with lower levels of total fat, saturated fat, and trans-fat (pro-inflammatory food parameters) intake among individuals (Kelly, 2010). This suggests that consuming a pro-inflammatory diet, rich in fat, would be associated with increased odds of developing hyperlipidemia. For example, high intake of palmitic acid, a common saturated fatty acid, can induce hyperlipidemia in adults (Miao et al., 2016).

Sex-stratified results showed that women who consumed pro-inflammatory diets had an increased risk of CVA. Specifically, small changes in the inflammatory potential of diet can significantly increase risk of CVA. A study by Fung et. al., found that women that consumed a healthy diet (resembling a Mediterranean diet) had a lower risk for stroke compared to women who consumed an energy-dense diet (RR=0.87, 95% CI: [0.73, 1.02]) (Fung et al., 2009).

Inflammation and oxidative stress can both be important mechanisms leading to endothelial dysfunction and arterial damage (Guzik & Touyz, 2017). Atherosclerosis is the buildup of plaque (fatty deposits) in the arteries (*American Heart Association: Artherosclerosis*, 2020). Inflammatory mediators are recognized as having an important role in the development of atherosclerosis. As previously mentioned, diets low an fat intake is associated with lower levels of inflammatory biomarkers (Estruch et al., 2006; Mazidi

et al., 2018). The microenvironment surrounding atherosclerotic plaque is typically characterized by a repeated inflammatory response. Specifically, this process involves the recruitment of macrophages, and lymphocytes to the affected area (Golia et al., 2014). Subendothelial accumulation of low-density lipoproteins (LDLs) cause endothelial injury that is necessary for the initiation of atherogenesis. LDLs become oxidized, exerting a pro-atherogenic effects (Golia et al., 2014; Welsh et al., 2017). Through this process several pro-inflammatory cytokines, such as IL-1, IL-8, and TNF-α, are released. Activated T lymphocytes initiate an inflammatory cascade and promote the amplification of pathways leading to plaque formation. However, it is the development of plaque then leads to plaque rupture and thrombosis (Golia et al., 2014). This typically occurs when plaque has thin fibrous caps (Libby, 2006). Inflammation can interfere with fibrous cap formation through blocking the creating of new collogen fibers and by stimulating the destruction of existing collagen. Specifically, T lymphocytes produce interferon- γ that inhibits collagen production. Additionally, T lymphocytes promote thrombosis. Therefore, inflammation promotes the initiation of atherosclerotic lesions and the progression of plaques; thinking of the fibrous caps, and thrombosis (Libby, 2006). Inflammation has a pivotal role in the plaque formation and thrombosis which are causally related to the development of CVD-related outcomes, especially CAD (Fioranelli et al., 2018; Steven et al., 2019). However, the time course of these outcomes varies. For example, hypertension can take several years to develop but a high salt intake can expedite this process (Van Vliet & Montani, 2008). Furthermore, some outcomes can take decades to develop. For example, atherosclerosis can persist for many years before plaques rupture causing thrombosis that could result in a cerebrovascular accident, such as stroke (Bentzon, Otsuka, Virmani, & Falk, 2014). In

addition, diet can operate through other mechanisms to promote the onset of CVD-related outcomes.

Our study had several limitations that need to be considered when interpreting these results. First, causal inference may be difficult due to the cross-sectional nature of the analysis. For example, in this study dietary intake information was gathered using FFQs, however, some CVD events preceded or followed of collection of dietary information. Therefore, a temporal relationship could not be established whether diet influenced CVD outcomes or if CVD diagnoses influenced dietary intake among participants. Second, the use of FFQ methodology to collect dietary information (in the past year) may have led to recall bias resulting in a greater degree of misinformation compared to other collection methods, such as 24-hr recalls. For example, individuals who are suffering from a chronic disease or with a family history of chronic disease, such as CVD, might recall past dietary exposure more accurately compared to healthy individuals. FFQs are prone to recall bias because participants are asked to report intake retrospectively and usually refer to prolonged time periods, such as 1 year in the 2005 Block FFQ (Naska, Lagiou, & Lagiou, 2017). In addition, intentional misreporting can lead to biased estimates of intake (i.e., social desirability bias) (Naska et al., 2017). Third, there was a potential for selection bias introduced based on the several levels of selective participation. For example, lack of dietary data may be characteristic of a subgroup within SJLIFE. This resulted in incomplete dietary information for many participants in SJLIFE that may be similar in some characteristics and different from participants that had available dietary information. Finally, confounding may be introduced by unknown/unmeasured variables related to the

association of interest. In addition, measurement bias may be present due to imprecise measurement of covariates.

Conclusion

Results from this study indicated that the E-DII is associated with certain CVD outcomes among SJLIFE participants, providing further evidence for the role of a nutrient-dense, anti-inflammatory diet in regulating chronic inflammation among this vulnerable population. Future research should be dedicated to understanding the complexity of the underlying mechanisms relating dietary inflammation, treatment associated cardiotoxicity, and cancer survivorship.

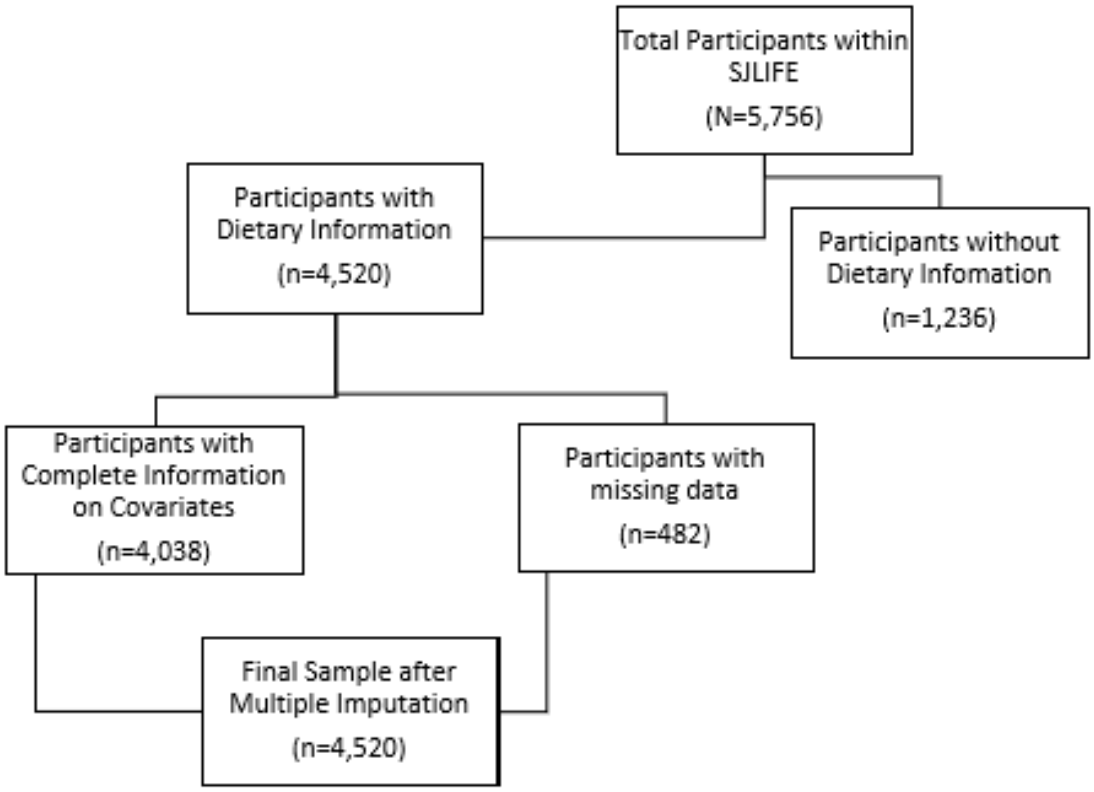

Figure 6-1. Study Sample

Table 6-1. CTCAE Grades

Cardiovascular Health Condition	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Hypertension	Prehypertension (SBP 120-139 mm Hg or DBP 80-89 mm Hg) from resting BP in HPL	Stage 1 hypertension (systolic BP 140 - 159 mm Hg or diastolic BP 90 - 99 mm Hg); medical intervention indicated or initiated; recurrent or persistent (>=24 hrs); symptomatic increase by >20 mm Hg (diastolic) or to >140/90 mm Hg if previously WNL; monotherapy indicated or initiated Pediatric: recurrent or persistent (>=24 hrs) BP >ULN; monotherapy indicated or initiated	Stage 2 hypertension (systolic BP >=160 mm Hg or diastolic BP >=100 mm Hg); medical intervention indicated; more than one drug or more intensive therapy than previously used indicated or initiated Pediatric: Same as adult	Life-threatening consequences (e.g., malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis); urgent intervention indicated Pediatric: Same as adult	Death
Hyperlipidemia Hypertriglyceridemia	150 mg/dL - 300 mg/dL	>300 mg/dL - 500 mg/dL; or treatment with a lipid	>500 mg/dL - 1000 mg/dL; or treatment with >=2	>1000 mg/dL; life-threatening consequences	Not applicable

		lowering agent	lipid lowering agents		
Hypercholesterolemia	>200 mg/dL - 300 mg/dL	>300 - 400 mg/dL; or treatment with one lipid lowering agent	>400 - 500 mg/dL; or treatment with >=2 lipid lowering agents	>500 mg/dL	Not applicable
Cardiomyopathy	Not applicable	Resting EF <50-40%; 10-19% drop from baseline	Resting EF 39-20%;≥20 % drop from baseline or intervention indicated or initiated	Resting EF <20% or with a history of EF <20% that has improved on subsequent ECHO after intervention initiated. Interventions may include ventricular assist devices, intravenous vasopressor support, or heart transplant	Not applicable
Coronary Artery Disease (CAD)	Not applicable	Asymptomatic and cardiac enzymes minimally abnormal and no evidence of ischemic ECG changes	Severe symptoms; cardiac enzymes abnormal; hemodynamically stable; ECG changes consistent with infarction (Q waves)	Life-threatening consequences; hemodynamically unstable (CARBG or angioplasty)	Death

Cardiac Dysrhythmia	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Symptomatic and incompletely controlled medically, or controlled with device (e.g., pacemaker), or ablation	Life-threatening consequences; urgent intervention indicated	Death
Cerebrovascular Accidents (CVA)	Mild	Moderate	Severe/disabling	Life-threatening	Death

Information represents the grading of CVD related outcomes among individuals in the SJLIFE study

Table 6-2. Distribution of characteristics across E-DII quartiles, St. Jude Lifetime Cohort Study, 2007-2012

DII Quartile (range)	Quartile 1 (-5.844, -1.497)	Quartile 2 (-1.497, 0.472)	Quartile 3 (0.472, 1.887)	Quartile 4 (1.887, 4.569)	
Characteristics	(N = 1130)	(N = 1130)	(N = 1130)	(N = 1130)	p-value[a,b]
Study Population					<.0001
Survivor	927 (82%)	975 (86%)	1011 (89%)	1019 (90%)	
Control	203 (18%)	155 (14%)	119 (11%)	111 (10%)	
Age (years)	30.6 (12.2)	29.5 (12.4)	28.9 (13.6)	27.6 (12.6)	<.0001
Sex					<.0001
Male	403 (36%)	569 (50%)	637 (56%)	722 (64%)	
Female	727 (64%)	561 (50%)	493 (44%)	408 (36%)	
Race/Ethnicity					<.0001
White	975 (88%)	930 (84%)	917 (83%)	890 (81%)	
Black	93 (8%)	149 (13%)	168 (15%)	197 (18%)	
Other	42 (4%)	34 (3%)	19 (2%)	18 (2%)	
Education					<.0001
0-12 Grade, did not graduate	34 (3%)	73 (7%)	108 (11%)	145 (14%)	
HS Diploma or GED	110 (11%)	182 (18%)	209 (21%)	293 (29%)	
Some College or Training	294 (29%)	363 (35%)	388 (39%)	392 (39%)	
College Graduate	571 (57%)	408 (40%)	298 (30%)	178 (18%)	
BMI (kg/m)					<.0001
<25	509 (45%)	439 (39%)	419 (37%)	493 (44%)	
25-30	324 (29%)	317 (28%)	357 (32%)	275 (24%)	
>30	297 (26%)	374 (33%)	354 (31%)	362 (32%)	
Smoking					<.0001
Ever Smokers	243 (22%)	293 (26%)	345 (31%)	432 (39%)	
Never Smokers	865 (78%)	814 (74%)	754 (69%)	666 (61%)	

Heavy Drinking					<.0001
Yes	51 (5%)	66 (6%)	107 (10%)	103 (10%)	
No	1047 (95%)	1031 (94%)	966 (90%)	974 (90%)	
Binge Drinking					
Yes	557 (50%)	489 (44%)	557 (51%)	566 (52%)	0.006
No	547 (50%)	614 (56%)	536 (49%)	526 (48%)	
Physical Activity					<.0001
Meets CDC	739 (65%)	590 (52%)	539 (48%)	490 (43%)	
Does not meet CDC	391 (35%)	540 (48%)	591 (52%)	640 (57%)	
Type of Cancer					<.0001
ALL	274 (24%)	319 (28%)	309 (27%)	278 (25%)	
CNS Tumors	91 (8%)	136 (12%)	163 (14%)	139 (12%)	
Hodgkin Lymphoma	142 (13%)	106 (9%)	106 (9%)	111 (10%)	
Sarcomas	104 (9%)	133 (12%)	125 (11%)	148 (13%)	
Embryonal Tumors	115 (10%)	103 (9%)	115 (10%)	157 (14%)	
Other	199 (18%)	176 (16%)	191 (17%)	184 (16%)	
No cancer	205 (18%)	157 (14%)	121 (11%)	113 (10%)	
Radiation					0.32
Yes	534 (47%)	551 (49%)	578 (51%)	555 (49%)	
No	596 (53%)	579 (51%)	552 (49%)	575 (51%)	
Cranial Radiation					0.02
Yes	209 (39%)	257 (47%)	263 (46%)	215 (39%)	
No	325 (61%)	294 (53%)	315 (54%)	340 (61%)	
Chest Radiation					0.37
Yes	14 (1%)	10 (1%)	20 (2%)	16 (1%)	
No	520 (99%)	541 (99%)	558 (98%)	539 (99%)	
Chemotherapy					0.09

Yes	458 (41%)	515 (46%)	480 (42%)	472 (42%)	
No	672 (59%)	615 (54%)	650 (58%)	658 (58%)	
Alkylating Agents					0.003
Yes	575 (51%)	637 (56%)	608 (54%)	657 (58%)	
No	555 (49%)	493 (44%)	522 (46%)	473 (42%)	
Anthracyclines					0.004
Yes	545 (48%)	556 (49%)	544 (48%)	618 (55%)	
No	585 (52%)	574 (51%)	586 (52%)	512 (45%)	
Antimetabolites					0.09
Yes	458 (41%)	515 (46%)	480 (42%)	472 (42%)	
No	672 (59%)	615 (54%)	650 (58%)	658 (58%)	
Hypertension					0.44
Yes	207 (18%)	225 (20%)	222 (20%)	238 (21%)	
No	923 (82%)	905 (80%)	908 (80%)	892 (79%)	
Hyperlipidemia					0.5
Yes	86 (8%)	76 (7%)	80 (7%)	68 (6%)	
No	1044 (92%)	1054 (93%)	1050 (93%)	1062 (94%)	

Data presented are median (IQR), N (%).
[a]Continuous Variables were compared using ANOVA
[b]Categorical Variables were compared using Chi-square test

Table 6-3. Odds Ratios and confidence intervals for association between E-DII and Hypertension, St. Jude Lifetime Cohort Study, 2007-2012

	Model 1[a]	Model 2[b]	Model 3[c]
(n=3259)	OR (95% CI)	OR (95% CI)	OR (95% CI)
E-DII (continuous)	1.03 (0.99, 1.06)	**1.06 (1.03, 1.10)**	1.02 (0.98, 1.06)
E-DII Quartiles			
Quartile 1	1.0 (ref)	1.0 (ref)	1.0 (ref)
Quartile 2	1.11 (0.90, 1.37)	1.21 (0.98, 1.51)	0.98 (0.86, 1.13)
Quartile 3	1.09 (0.88, 1.35)	1.21 (0.97, 1.50)	0.95 (0.83, 1.09)
Quartile 4	1.19 (0.97, 1.46)	**1.46 (1.17, 1.81)**	1.11 (0.97, 1.28)

Data presented are Odds Radios (95% CI).

[a]Unadjusted Model (CRP = E-DII)

[b]Age-adjusted Model

[c]Multivariable Model: adjusted for age, gender, race, education, BMI, smoking, heavy drinking, PA, study population, alkylating agents, antimetabolites, and chest radiation.

Table 6-4. Odds Ratios and confidence intervals for association between E-DII and Hyperlipidemia, St. Jude Lifetime Cohort Study, 2007-2012

	Model 1[a]	Model 2[b]	Model 3[c]
	OR (95% CI)	OR (95% CI)	OR (95% CI)
E-DII (continuous)	0.96 (0.91, 1.01)	0.96 (0.91, 1.02)	**0.91 (0.86, 0.97)**
E-DII Quartiles			
Quartile 1	1.0 (ref)	1.0 (ref)	1.0 (ref)
Quartile 2	0.88 (0.64, 1.21)	0.89 (0.65, 1.23)	0.96 (0.78, 1.18)
Quartile 3	0.93 (0.67, 1.27)	0.95 (0.69, 1.30)	0.99 (0.80, 1.21)
Quartile 4	0.78 (0.56, 1.08)	0.81 (0.58, 1.13)	0.80 (0.64, 1.003)

Data presented are Odds Radios (95% CI).

[a]Unadjusted Model (CRP = E-DII)

[b]Age-adjusted Model

[c]Multivariable Model: adjusted for age, gender, race, education, BMI, smoking, heavy drinking, PA, study population, alkylating agents, and chest radiation.

Table 6-5. Odds Ratios and confidence intervals for association between E-DII and Cardiomyopathy, St. Jude Lifetime Cohort Study, 2007-2012

	Model 1[a]	Model 2[b]	Model 3[c]
	OR (95% CI)	OR (95% CI)	OR (95% CI)
E-DII (continuous)	1.02 (0.96, 1.07)	1.01 (0.95, 1.07)	0.97 (0.91, 1.04)
E-DII Quartiles			
Quartile 1	1.0 (ref)	1.0 (ref)	1.0 (ref)
Quartile 2	0.91 (0.64, 1.29)	0.89 (0.62, 1.27)	0.92 (0.73, 1.15)
Quartile 3	1.03 (0.73, 1.46)	1.01 (0.71, 1.42)	1.02 (0.82, 1.26)
Quartile 4	1.08 (0.77, 1.52)	1.04 (0.73, 1.46)	0.96 (0.77, 1.20)

Data presented are Odds Radios (95% CI).

[a]Unadjusted Model (CRP = E-DII)

[b]Age-adjusted Model

[c]Multivariable Model: adjusted for age, gender, race, education, BMI, smoking, heavy drinking, PA, anthracyclines, and chest radiation.

Table 6-6. Odds Ratios and confidence intervals for association between E-DII and Coronary Artery Disease (CAD) , St. Jude Lifetime Cohort Study, 2007-2012

	Model 1[a]	Model 2[b]	Model 3[c]
	OR (95% CI)	OR (95% CI)	OR (95% CI)
E-DII (continuous)	1.08 (0.997, 1.17)	**1.14 (1.05, 1.24)**	1.09 (0.99, 1.20)
E-DII Quartiles			
Quartile 1	1.0 (ref)	1.0 (ref)	1.0 (ref)
Quartile 2	1.58 (0.95, 2.63)	**1.85 (1.10, 3.10)**	1.14 (0.84, 1.55)
Quartile 3	**1.96 (1.20, 3.20)**	**2.30 (1.39, 3.81)**	**1.34 (1.003, 1.80)**
Quartile 4	1.45 (0.87, 2.44)	**1.97 (1.16, 3.35)**	0.99 (0.72, 1.38)

Data presented are Odds Radios (95% CI).

[a]Unadjusted Model (CRP = E-DII)

[b]Age-adjusted Model

[c]Multivariable Model: adjusted for age, gender, race, education, BMI, smoking, heavy drinking, PA, hypertension, and hyperlipidemia.

Table 6-7. Odds Ratios and confidence intervals for association between E-DII and Dysrhythmia, St. Jude Lifetime Cohort Study, 2007-2012

	Model 1[a]	Model 2[b]	Model 3[c]
	OR (95% CI)	OR (95% CI)	OR (95% CI)
E-DII (continuous)	0.97 (0.87, 1.07)	0.99 (0.90, 1.09)	1.02 (0.92, 1.13)
E-DII Quartiles			
Quartile 1	1.0 (ref)	1.0 (ref)	1.0 (ref)
Quartile 2	0.66 (0.37, 1.17)	0.70 (0.39, 1.24)	0.81 (0.55, 1.18)
Quartile 3	0.86 (0.51, 1.47)	0.92 (0.54, 1.57)	1.12 (0.79, 1.59)
Quartile 4	0.69 (0.40, 1.22)	0.79 (0.45, 1.39)	0.98 (0.66, 1.45)

Data presented are Odds Radios (95% CI).

[a]Unadjusted Model (CRP = E-DII)

[b]Age-adjusted Model

[c]Multivariable Model: adjusted for age, gender, race, education, BMI, smoking, heavy drinking, PA, hypertension, and chest radiation.

Table 6-8. Odds Ratios and confidence intervals for association between E-DII and Cerebrovascular Accident (CVA), St. Jude Lifetime Cohort Study, 2007-2012

	Model 1[a]	Model 2[b]	Model 3[c]
	OR (95% CI)	OR (95% CI)	OR (95% CI)
E-DII (continuous)	1.08 (0.98, 1.19)	1.09 (0.99, 1.20)	1.03 (0.92, 1.14)
E-DII Quartiles			
Quartile 1	1.0 (ref)	1.0 (ref)	1.0 (ref)
Quartile 2	**2.32 (1.23, 4.38)**	**2.36 (1.26, 4.46)**	1.29 (0.92, 1.80)
Quartile 3	**2.10 (1.10, 4.00)**	**2.15 (1.13, 4.09)**	1.10 (0.79, 1.55)
Quartile 4	1.80 (0.93, 3,49)	1.88 (0.99, 3.64)	0.99 (0.68, 1.44)

Data presented are Odds Radios (95% CI).

[a]Unadjusted Model (CRP = E-DII)

[b]Age-adjusted Model

[c]Multivariable Model: adjusted for age, gender, race, education, BMI, smoking, heavy drinking, PA, and cranial radiation.

Table 6-9. Odds Ratios and 95% CI for CVD Outcomes by E-DII Quartiles Stratified by Sex, St. Jude Lifetime Cohort Study, 2007-2012

	Quartile 1	Quartile 2	Quartile 3	Quartile 4
Male				
Hypertension[a]	ref	1.20 (0.84, 1.72)	1.01 (0.70, 1.46)	1.37 (0.95, 1.96)
Hyperlipidemia[b]	ref	0.96 (0.58, 1.58)	0.91 (0.55, 1.51)	0.74 (0.48, 1.26)
Cardiomyopathy[c]	ref	0.99 (0.56, 1.74)	0.94 (0.53, 1.67)	0.90 (0.51, 1.60)
CAD[d]	ref	1.87 (0.78, 4.49)	1.87 (0.78, 4.52)	1.35 (0.54, 3.35)
Dysrhythmia[e]	ref	0.70 (0.25, 1.94)	0.66 (0.23, 1.88)	0.56 (0.19, 1.69)
CVA[f]	ref	0.59 (0.21, 1.61)	0.92 (0.37, 2.30)	0.92 (0.36, 2.31)
Female				
Hypertension[a]	ref	0.87 (0.62, 1.20)	0.92 (0.65, 1.29)	0.98 (0.67, 1.43)
Hyperlipidemia[b]	ref	0.62 (0.36, 1.05)	0.63 (0.36, 1.11)	0.62 (0.33, 1.15)
Cardiomyopathy[c]	ref	0.68 (0.40, 1.16)	0.70 (0.40, 1.23)	0.74 (0.41, 1.34)
CAD[d]	ref	1.05 (0.41, 2.69)	2.10 (0.85, 5.21)	1.10 (0.36, 3.41)
Dysrhythmia[e]	ref	0.63 (0.28, 1.37)	0.95 (0.44, 2.04)	1.08 (0.48, 2.44)
CVA[f]	ref	**5.71 (1.86, 17.53)**	2.70 (0.77, 9.43)	1.67 (0.38, 7.31)

Data presented are OR (95% CI).

[a]Adjusted for age, race, education, BMI, smoking, heavy drinking, PA, alkylating agents, antimetabolites, and chest radiation.

[b]Adjusted for age, race, education, BMI, smoking, heavy drinking, PA, alkylating agents, and chest radiation.

[c]Adjusted for age, race, education, BMI, smoking, heavy drinking, PA, anthracyclines, and chest radiation.

[d]Adjusted for age, race, education, BMI, smoking, heavy drinking, PA, hypertension, and hyperlipidemia.

[e]Adjusted for age, race, education, BMI, smoking, heavy drinking, PA, hypertension, and chest radiation.

[f]Adjusted for age, race, education, BMI, smoking, heavy drinking, PA, and cranial radiation.

CHAPTER 7

SUMMARY

7.1 Understanding the Dietary Inflammatory Index

The Dietary inflammatory index (DII®) was developed to provide a tool to assess the inflammatory potential of adults' diet (Cavicchia et al., 2009). The DII has applications that exceed its original intention as a research tool. For example, it can also be used: 1) as a basis for designing interventions to change individuals' dietary choices and inform them about the effect food items can have on regulating diet-induced inflammation (G. M. Turner-McGrievy et al., 2019; M. D. Wirth et al., 2020); 2) to compare menus and recipes from different culinary traditions (Steck et al., 2014) or based on recommended diets (G. Turner-McGrievy, Wirth, Hill, Dear, & Hébert, 2021);. and 3) as a means to evaluate the relative capacity of different foods to influence inflammation (Hébert et al., 2019). Thus, the DII and its various derivatives can provide a way to evaluate the association between diet and a variety of health outcomes as well as actionable advice and products to promote better health and well-being.

The improved version of the DII (i.e., DII Gen2) that has now been used as the basis of over 500 peer-reviewed publications was developed from 2009 to 2014. Compared to the original DII (i.e., DII Gen1), which was developed from 2004 to 2009, DII Gen2 is based on a refined scoring algorithm derived from almost 2,000 articles related to associations between macro- and micro-nutrient intakes and inflammatory biomarker

(Shivappa et al., 2014). The scoring system is comprised of 45 parameters that consisted of nutrients, whole food items, and other dietary compounds. In order to represent a wide range of dietary intakes from around the world, 11 dietary intake databases were used to create a composite (referent) database with the intention of serving as comparable intake values for each food parameter. The scoring system implemented in the DII created centered-proportions values that were multiplied by actual intakes to estimate every individuals' DII score. Inconsistencies among some populations led to the realization that energy intake can distort results based on the DII. For example, there is a tendency of individuals to eat more of both nutrient-dense and energy-dense foods as energy intake increases (Hébert et al., 2019). For this reason, the Energy-adjusted DII (E-DII™) was created to better fit some populations of interest. Upon having begun my doctoral program, it would take several conversations with my academic advisor (spanning several years) and taking my first nutritional epidemiology class to better understand the design and novelty of this tool. When deciding which doctoral program to attend, it was the research interests and track record of my academic advisor, Dr. James Hebert, that helped me make my final decision to attend the University of South Carolina (UofSC). I had become interested in childhood obesity, diet, and associated-health outcomes from my own experience with being overweight as a child and into adolescence. My academic advisor helped foster my desire to learn more about the field of child nutrition and health. Furthermore, my graduate assistantship spanning from 2016-2017 involved the development of the Children's DII (C-DII™). It was through this process that I began to understand the value of diverse mean intakes from various populations in creating a reliable composite database. Toward the end

of this assistantship, we all published a paper on the development of the C-DII (my first publication).

Following my work with the C-DII, I became very interested in childhood cancer incidence, mortality, and survival stemming from several conversations with my academic advisor. We discussed the implications of poor nutrition among childhood cancer survivors that would ultimately culminate in the development of a variety of comorbidities. Going forward I was focused on learning more about the burden childhood cancer could have on the physical, mental, and emotional health of patients and survivors. As my interest grew, so did my desire to find research opportunities in the field of childhood cancer. Upon completion of my qualifying exam, my advisor and I began discussing potential dissertation topics that I was interested in. Dr. Hebert knew of my interest in childhood cancer and insisted I research potential databases relevant information.

7.2 Gaining Access to the St. Jude Lifetime Cohort Study

At this juncture, I learned about St. Jude Children's Research Hospital (SJCRH). Its founder, Danny Thomas, often prayed to St. Jude (the patron saint of desperate cases and lost causes) in times of hardships. He experienced the power of prayer many times and dreamt of building a "shrine" to St. Jude. His dreams were realized when SJCRH was founded in 1960 to investigate the causes of childhood cancer and to provide treatment to individuals diagnosed with malignancies. It was during my search and becoming familiar with SJCRH that I first came upon the St. Jude Childhood Cancer Survivorship Study (CSS). I was disappointed to learn that this study had very little diet-related data for survivors. However, I was pleased to find information on another study currently being performed at SJCRH that had available dietary information, the St. Jude Lifetime Cohort

Study (SJLIFE). The SJLIFE study forms the basis for this dissertation. It began in 2007 at the St. Jude Children's Research Hospital (SJCRH). SJCRH is a NCI-designated comprehensive cancer center that is dedicated to the treatment of childhood cancer and provides medical services for child and adolescent cancer patients (Howell et al., 2020). Today, this cohort includes individuals who have a minimum of 5-years of survival who were diagnosed (1962-2012) and treated at SJCRH. SJLIFE participants are followed prospectively to perform ongoing medical assessments. These survivors are invited for follow-up at 5-year intervals following their initial recruitment into the study.

Upon several discussions with my academic advisor, we decided to apply for access to the data and investigate potential associations between the DII and detrimental outcomes among these childhood cancer survivors. I first contacted St. Jude in November 2017. I spoke with a few faculty members before discussing my interest in the inflammatory potential of diet and adverse health outcomes among childhood cancer survivors with Dr. Kirsten Ness. Following initial contact with Dr. Ness, it would be months before I would be ready to begin the dissertation process. My academic advisor and I finally had a chance to speak with Dr. Ness about collaborating on my research project in October 2018. It was at this meeting where Dr. Ness provided insight into the data application process. This process included completion of an approved concept proposal and presentations to the Epidemiology and Biostatistics Working Group, the Global Outcomes committee, and the Cancer Control and Survivorship Program (CCSP) in order to gain access to the data. After several rounds of revisions, my concept proposal was finally approved by Dr. Ness and the presentation of my proposal was the next step. I was able to present to all committees by

February 2020. After receiving approval, the process of gaining access to the actual data took several months but I finally gained access to the data in June 2020.

7.3 Specific Aims of Dissertation

I proposed investigating the association between the inflammatory potential of diet and inflammatory and metabolic markers for my Aim 1 to the members of my committee and it was accepted. Throughout the process of completing Aim 1 is where I began to familiarize myself with the SJLIFE data. The only inflammatory biomarker available in the SJLIFE data was C-reactive protein (CRP). Fortunately, the literature on CRP is more robust than virtually any other biomarker of inflammation (Brenner et al., 2014). Non-significant associations were observed for CRP as a continuous, binary, and categorical variable. Metabolic health was assessed through the following: hemoglobin A1C, fasting glucose, fasting insulin, the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR), high-density lipoprotein cholesterol (HDL), triglycerides, waist circumference, and metabolic syndrome (MetS). Each metabolic health outcome was either dichotomized or categorized for analysis. Significant associations were observed for the HOMA-IR and HDL levels. In addition, the analysis of metabolic health outcomes was stratified by sex on the basis of previous research. Among men, significant associations were observed between a pro-inflammatory diet and the HOMA-IR and triglyceride levels. Among women, significant associations were observed between a pro-inflammatory diet and the HOMA-IR and HDL levels.

For Aim 2, I proposed investigating the association between the inflammatory potential of diet and mental health outcomes (anxiety and depression) to my committee members and it was accepted. Symptoms of anxiety and depression were analyzed as

continuous and dichotomous response variables based on the Brief Symptom Inventory-18 (BSI-18). Non-significant associations were observed between a pro-inflammatory diet and symptoms of anxiety. In contrast, a pro-inflammatory diet was significantly associated with depressive symptoms. In addition, the analysis of anxiety and depression was stratified by sex on the basis of previous research. Neither men or women were observed to have significant associations between a pro-inflammatory diet and symptoms of anxiety. Among men, a pro-inflammatory diet was significantly associated with depressive symptoms. However, among women, non-significant associations were observed between a pro-inflammatory diet and depressive symptoms.

Finally, for Aim 3, I proposed investigating the association between the inflammatory potential of diet and cardiovascular health to my committee members and it was accepted. Cardiovascular health was assessed through the following: hypertension, hyperlipidemia, cardiomyopathy, coronary artery disease (CAD), cardiac dysrhythmia, and cerebrovascular accidents (CVA). A pro-inflammatory diet was inconsistently associated with hypertension, hyperlipidemia, CAD, and CVA. However, no associations were observed between a pro-inflammatory diet and cardiomyopathy or cardiac dysrhythmia. In addition, as for the previous outcomes, the analysis of cardiovascular health was stratified by sex based on previous research. Among women, inconsistent associations were observed between a pro-inflammatory diet and CVA. However, no significant associations were observed between a pro-inflammatory diet and cardiovascular health among men.

In the process of completing the literature review of childhood cancer and survivorship, I had noted that cardiovascular health is of paramount importance in this population. Childhood cancer survivors are approximately seven times more likely than

individuals from the general population to suffer from CVD-related mortality (Armenian et al., 2018). Furthermore, metabolic health outcomes, such as MetS, were associated with an increased risk of CVD in this population (Pluimakers, van Waas, Neggers, & van den Heuvel-Eibrink, 2019; W. A. Smith et al., 2014). Mental health outcomes, such as anxiety and depression, are also associated with CVD outcomes among childhood cancer survivors (Friend et al., 2018; Vuotto et al., 2017). These associations prompted my interest in investigating them for this dissertation. So, obtaining results that were not consistent with previous literature, led me to consider what might be going on and how we can address these important issues in the future.

7.4 Future Research

Further knowledge is needed on the impact of a pro-inflammatory diet on biomarkers of inflammation. The SJLIFE study had a small sample of survivors with CRP information. CRP was the only inflammatory biomarker available among the cohort. Furthermore, as an acute phase protein it presents problems in terms of natural variations in timing and a relatively high variance; making it difficult to detect an effect in a relatively small sample of individuals (Dorraki et al., 2018). SJLIFE can pursue expansion of its comprehensive clinical assessments to include measurements of other inflammatory biomarkers, such as IL-1β, IL-4, and TNF-α. Previous research has used different biomarkers of inflammation to validate the DII (Hébert et al., 2019; Tabung et al., 2015; Vahid et al., 2018; M. D. Wirth, Shivappa, Davis, et al., 2017). Another option is to expand the evaluation of CRP among SJLIFE participants in order to increase this subsample. However, there would be a need to collect samples near the same time that dietary information is being collected. Presence of infections can also require limiting the analysis

to samples of CRP < 10 mg/L (Dhingra et al., 2007; Perry et al., 2020; Villaseñor et al., 2014).

Information bias can become problematic when estimating dietary intakes from Food Frequency Questionnaires (FFQs). Self-reported assessments of dietary intakes are usually hindered by the inaccurate reporting of intakes (Shim, Oh, & King, 2014). Among childhood cancer survivors, underreporting can become an issue in gathering accurate information. This group of survivors tend to significantly underreport intakes in FFQs compared to intakes reported through the use of other self-reported measures, such as 24-hr diet recalls (24HRs), 22% and 1%, respectively (F. F. Zhang, Roberts, et al., 2015). In addition, gender differences have been observed in the accuracy of responses (Hebert, Clemow, Pbert, Ockene, & Ockene, 1995; Hebert et al., 2002, 1997). It would be advantageous for SJLIFE to incorporate 24HRs into their collected information. This would more accurately represent their true intakes and provide better inference for research and intervention strategies. Although this would be very expensive, administering a 24HR to a subset of participants could provide validation of this dietary assessment method with inflammatory biomarkers among this group of survivors.

This research focused on childhood cancer survivors of all subtypes. Aim 2 focused on the association between a pro-inflammatory diet and symptoms of anxiety and depression among all survivors. However, specific subgroups of survivors may be more susceptible to health outcomes investigated in this study. For example, empirical evidence suggests that survivors of central nervous system (CNS) tumors have a greater risk of adverse mental health outcomes compared to survivors of other cancer subtypes (Friend et al., 2018). Furthermore, treatment methods used on childhood cancer patients can elevate

the risk of adverse mental health. For example, cranial radiation and anthracycline administration can increase the risk of suffering from adverse mental health problems compared to individuals that did not receive these forms of treatment (Friend et al., 2018). Future research can focus on the association of a pro-inflammatory diet and mental health outcomes among subgroups of childhood cancer survivors that would receive the greatest benefit from intervention strategies.

This research has focused on the association between the inflammatory potential of diet and adverse health outcomes using a cross-sectional approach. A subsample of SJLIFE participants have information from multiple follow-up visits. To establish a temporal relationship between the DII/C-DII and health outcomes, a longitudinal approach toward investigating this association is needed in order to address potential reverse causality. For example, information used in this study was gathered before or at the time the participants also completed the FFQ. This made it difficult to ascertain whether their diet over the past year influenced their outcomes or if their outcomes influenced their dietary intake (did they change their diet to regulate their condition?).

Finally, this cohort was previously comprised of childhood cancer survivors who were at least 18 years old and had survived for a minimum of 10 years. However, in 2015 the cohort was expanded to include childhood cancer survivors of all ages who had survived for a minimum of 5 years. As briefly mentioned, the C-DII was created to assess the inflammatory potential of diet among children and adolescents 6-14 years old. A new composite database was created based on the consumption of macro- and micronutrients among children and adolescents from 16 different countries. The C-DII has been validated among children and adolescents from the U.S. National Health and Nutrition Examination

Survey (NHANES) using CRP concentrations (Khan et al., 2018). This tool can be used to investigate the associations between the inflammatory potential of diet and adverse health events among childhood cancer survivors in this younger age group. Furthermore, interventions can target this subgroup of childhood cancer survivors and instill better health practices from an early age and reduce their risk for detrimental outcomes. Specifically, a DII-based intervention approach.

7.5 Problems faced and lessons learned

This dissertation is a scientific document that was written over countless hours of work spanning from 2018 to 2021. This process involved writing in a scientific manner, gathering knowledge, refining ideas, performing statistical analyses, reporting results, and drawing inferences based on my findings. All of the components involved has helped me become a better scientist and epidemiologist. My hope is that this dissertation will provide a linear record of the process and provide insight that may be useful to future students. Here are my recommendations to them.

Start Early: As has been discussed, the process of making contact and gaining access to datasets of interest can take a long time. It is important for future doctoral students to begin thinking of dissertation topics as early as feasible so that they can identify relevant sources of data. Making initial contact with St. Jude was the first step. However, it would take time to gain access to the data. The process of reaching out to researchers with whom you do not have a personal relationship can be difficult. I had to take the initiative to schedule an in-person meeting with Dr. Ness at SJCRH in Memphis, TN in order to create a more personal interest in this topic. Following our first in-person meeting the process was expedited substantially.

Schedule your time: Throughout this process many obstacles and competing responsibilities have impacted my ability to complete this dissertation in a timely manner. I cannot overemphasize creating schedules for yourself and sticking to them. This realization came to me as a teaching assistant/graduate assistant at UofSC, and later as an assistant professor at the University of Texas Health Science Center at Tyler (UTHSCT). There were competing interests from work, school, and personal responsibilities. Having a schedule helped me balance all of these components in my daily life.

Make daily goals: The amount of work required to complete a dissertation is tremendous. As a student (pre-dissertation) you understand that it will be difficult, but it is not until you are in the process that you truly understand and respect the work that many have done before you. At times, this process can feel overwhelming. It is important that future students make daily goals for themselves. Students will need to understand that there is a limit to what can be accomplished each day but also that making daily goals is pivotal to your advancement towards completion. Furthermore, it is important that students orient their daily goals towards meeting self-imposed deadlines but also to remain open to readjustments. For example, I would set daily goals with the intention of completing a chapter and submitting that chapter to my committee on a pre-determined date. Of course, obstacles can present themselves and you will not be able to meet every single deadline but through imposing these small deadlines that we achieve our ultimate goal of completion.

Ask for feedback regularly: It is important to remain in contact with your committee throughout this experience. For example, I had worked on sections of my dissertation (e.g., Introduction and Methods)) for each chapter ahead of running the analyses. However, I did not ask for thorough feedback from all committee members before

submitting my chapter 4 draft. This made it so feedback and edits for my draft felt insurmountable upon reading. So, to avoid this dilemma I urge future students to ask for constant feedback from their respective committees.

Do not take criticism personally: This relates to my previous point above. Some feedback you receive may feel unreasonable and unrelenting. It is important that students understand that your committee is here to guide and support you. The feedback they provide and the edits they suggest are directed towards your improvement as an academic researcher and professional. So, please do your best to not take it personally.

Protect your mental well-being: As mentioned before this process can feel overwhelming and harsh criticism can make you lose confidence in your own ability to succeed. However, it is important that you make sure to protect your mental health. Taking breaks from your work is important for you to recover from the stress it produces. Dedicating time to taking care of your overall wellbeing will substantially improve the symptoms of psychological distress that you may be experiencing. After the first found of feedback I was unsure if I would be able to successfully complete the process. My partner suggested getting a couple's massage to de-stress and get away from my computer. These interludes can help you reinvigorate your desire to succeed and reaffirm that you are where you should be.

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